AD_____

Award Number: DAMD17-98-D-0032

TITLE: Preclinical Pharmacodynamic and Pharmacokinetic Studies of Investigational New Drugs

PRINCIPAL INVESTIGATOR: Patricia E. Noker, Ph.D.

CONTRACTING ORGANIZATION: Southern Research Institute
Birmingham, Alabama 35205-5305

REPORT DATE: October 2002

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2002	Annual (8 Sep 01 - 7 Sep 02)

4. TITLE AND SUBTITLE
Preclinical Pharmacodynamic and Pharmacokinetic Studies of Investigational New Drugs

5. FUNDING NUMBERS
DAMD17-98-D-0032

6. AUTHOR(S)
Patricia E. Noker, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Southern Research Institute
Birmingham, Alabama 35205-5305

E-Mail: noker@sri.org

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

A study was conducted to investigate the pharmacodynamic effects, as assessed by signs of clinical and pathological toxicity, of artelinate (AL; given as an L-lysine salt) and artesunate (AS) in male and female Sprague-Dawley rats given single or multiple intravenous (iv) doses via a tail vein; intramuscular (im) administered arteether (AE) served as the positive control for the formation of neurotoxicological lesions. For rats given single iv doses, mortality was observed at AL doses of ≥160 mg/kg and at an AS dose of 400 mg/kg. Following 7 consecutive days of iv dose administration, no mortality was observed for male and female rats given ≤37.5 mg/kg/day of AL (total dose: ≤262.5 mg/kg) or ≤75 mg/kg/day of AS (total dose: ≤525 mg/kg). Due to the difficulty encountered during the iv administration of AL, no conclusions could be drawn relative to the lethality produced by higher multiple iv doses of AL. Single or multiple iv dose administration of AL produced a possible dose-dependent venotoxicity that was characterized by black and/or dark discoloration of the tail, which in some instances was accompanied by necrosis. Clinical pathological changes observed for rats given iv doses of 80 mg/kg/day of AL for ≤4 days or 150 mg/kg/day of AS for 7 consecutive days were consistent with an effect on hematopoiesis. No evidence was obtained for the presence of histopathological lesions in the hindbrains of rats given ≤37.5 mg/kg/day of AL for 7 consecutive days or ≤150 mg/kg/day of AS for 7 consecutive days.

14. SUBJECT TERMS	15. NUMBER OF PAGES
artelinate, artesunate, arteether, iv, rats, pharmacodynamics, toxicity, neuropathy, investigational drugs	80
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Page

Cover Page.....1

Standard Form 298.....2

Table of Contents.....3

1.0 Introduction.....4

2.0 Research Accomplishments for Each Task Order.....5

2.1 Task Order SR01-1: Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats.....5

3.0 Key Research Accomplishments.....21

4.0 Reportable Outcomes.....22

5.0 Conclusions.....22

6.0 References.....23

1.0 INTRODUCTION

The work scope of this contract involves the performance of studies in rats and dogs on the pharmacokinetic and pharmacodynamic properties of drugs under clinical development by the U.S. Army Medical Research and Development Command. The pharmacokinetic aspect of these studies involves an investigation of the absorption, disposition, metabolism (biotransformation), and elimination of test compounds in experimental animals. The pharmacodynamic aspect involves relating certain measured parameters, for example, the production of methemoglobin, to blood and plasma levels of the test compound and/or its metabolites, or assessing toxicological parameters such as adverse clinical signs and mortality that occur after administration of a test compound. The information derived from these studies is intended to provide a data base for establishing an appropriate species and appropriate doses for subsequent subchronic and chronic toxicity studies, to predict for possible organ toxicities which might occur, and to generate data required by the Food and Drug Administration prior to submission of a Notice of Claimed Investigational Exemption for a New Drug (IND) and New Drug Applications, Human Use (NDA).

During the past year of the contract, a study was conducted to investigate the pharmacodynamic effects of artelinate and artesunate, as assessed by signs of clinical and pathological toxicity, following daily intravenous administration to rats for 1 or 7 consecutive days.

2.0 RESEARCH ACCOMPLISHMENTS FOR EACH TASK ORDER

2.1 Task Order SR01-1: Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

2.1.1 Background and Objectives

Early in this century, with the discovery of quinine, malaria appeared to be one of the few diseases for which a specific cure existed. As a result, however, of the development of insecticide resistance by the Anopheles mosquito and the development by this parasite of resistance to chloroquine and mefloquine, malaria remains a major health problem in many areas of the world.[1] Qinghaosu (QHS), also known as artemisinin, was initially isolated and characterized by the Chinese and found to be an effective antimalarial agent.[2] This compound is a sesquiterpene lactone with an endo-peroxide bridge. The methyl ether (artemether) of reduced QHS, dihydroqinghaosu (DQHS), and the succinate hemiester of DQHS, artesunic acid, are also effective in the treatment of severe cases of multi-drug resistant malaria.[3] In addition, artelinic acid, a semisynthetic water-soluble derivative of QHS, has been reported to be effective against chloroquine-resistant P. falciparum and to be superior to QHS against P. berghei.[4]

Artemisinin derivatives differ from quinine/quinidine, the traditional treatments of severe malaria, in that they kill parasites much more rapidly. In that most mortality from severe malaria occurs in the first 24-48 hours, this class of compounds should theoretically reduce the mortality rate. The results of several large well-controlled studies, however, do not support this. It has been proposed that the lack of improvement may be due to slow and/or poor absorption following intramuscular administration of these oil soluble derivatives. Artesunate suppositories are being developed for initiation of treatment of critically ill patients where medical facilities are not available; however, bioavailability and variability of absorption is also an issue with suppositories.

An intravenous (iv) formulation ensures 100% bioavailability with immediate peak concentrations. Intravenous artesunate (AS) is currently available in China; however, only artelinate (AL) appears to have sufficient stability in solution to allow the drug to be available in a "ready-to-use" injection vial. The currently marketed AS formulation is a freeze-dried preparation, which requires mixing with a sodium bicarbonate solution at the bedside and then dilution with dextrose in water.[5] An artelinate/lysine formulation has recently been developed and is being evaluated for suitability as an iv injectable solution.

The objective of the task order was to conduct a dose-range finding evaluation of the pharmacodynamic effects of AL and AS, as assessed by signs of clinical and pathological toxicity, following iv administration of either compound to rats for 7 consecutive days. During the initial phase of this task order, an estimate of the single dose acute toxicity (LD_{50}) of iv administered AL or AS was obtained. This information was used to determine doses of AL or AS to be given during a subsequent 7 day range finding toxicity study involving the administration of AL, AS, or arteether (AE), as the positive control agent.

2.1.2 Materials and Methods

2.1.2.1 Test System

Male and female Sprague-Dawley rats were purchased from Charles River Laboratories, Inc. (Raleigh, NC; Area R05) and were received in 3 separate shipments for use in the different phases of the study. All rats in each shipment were 6-8 weeks old when they arrived at Southern Research Institute (Southern Research). Individual animal identification was by ear punch.

Upon arrival, the rats were placed in quarantine. The animals were examined for general health within 3 days of receipt. There were no significant findings indicative of poor health, and the animals were released for study. Each rat was allowed access to feed (Certified Rodent Diet #5002; PMI Feeds, Inc.; St. Louis, MO) and tap water (Birmingham public water supply) *ad libitum* during the quarantine and study periods. During both the quarantine and study periods, the rats were individually housed in solid-bottom polycarbonate shoebox cages supported on stainless steel racks in an animal room that was maintained at a temperature of 71.2-75.7 °F and a relative humidity of 49.0-80.0%. Excursions outside the desired relative humidity range (50±20%) that occurred were brief and did not affect the outcome of the study. Hardwood chip bedding (P.J. Murphy Forest Products, Inc.; Montville, NJ) was used in the cages for excrement absorption. Room lights were controlled by an automatic timer set to provide 12 hours of light (0600 to 1800 hours, CST) and 12 hours of dark per day. Cage size and animal care conformed to the Guidelines for the Care and Use of Laboratory Animals, 7th edition[6] and the U.S. Department of Agriculture through the Animal Welfare Act (Public Law 99-198).

2.1.2.2 Test Articles

Test Articles: One bottle containing 30 grams of artelinic acid/lysine salt (AL/lysine; WR 255663; Bottle No. BP21847; manufacturer's code 2117-308) was supplied by Walter Reed Army Institute of Research (WRAIR; Washington, DC). The bulk quantity of AL/lysine was stored frozen (-20 °C) from the time of receipt until the time of use and was assumed to be stable when so stored.

One bottle containing 200 grams of artesunic acid (artesunate; AS; WR 256283; Bottle No. BP18288; Lot No. 1 03) was supplied by WRAIR. The bulk quantity of AS was stored frozen (-20 °C) from the time of receipt until the time of use and was assumed to be stable when so stored.

One bottle containing 3 grams of arteether (AE; WR 255131; manufacturer's code FJ18-97-3) was supplied by WRAIR. The bulk quantity of AE was stored refrigerated from the time of receipt until the time of use and was assumed to be stable when so stored.

Dose Formulation Preparation: AL/lysine: The AL/lysine salt prepared by WRAIR was used for preparation of all dose formulations of AL; the preformulated AL/lysine salt contained 1 gram of artelinic acid per 1.35 g of salt.

Dose formulations of AL/lysine containing 4, 8, 16, 32, or 64 mg/mL of AL were prepared for use during the LD_{50} phase of the study. For this, stock solutions containing either 16 or

64 mg/mL of AL were prepared by dissolving a calculated quantity of AL/lysine salt in 0.9%NaCl/0.3% purified L-lysine. The 64 mg/mL AL/lysine solution was diluted to 32 mg/mL using 1 volume of 0.9% NaCl/0.3% purified L-lysine. The 16 mg/mL AL/lysine solution was diluted to 4, 8, or 16 mg/mL of AL using the appropriate volume of 0.9% saline/0.3% purified L-lysine.

Dose formulations containing 0.75, 1.5, 3, or 6 mg/mL of AL were prepared for use during the range-finding phase (Phases 2 and 3) of the study. These formulations were prepared by dissolving individual weighed quantities of AL/lysine salt in 0.9% NaCl/0.3% purified L-lysine.

The AL vehicle control dose formulations (0 mg/mL AL) contained 1.15% L-lysine monohydrochloride in 0.9% saline.

Each AL/lysine and corresponding vehicle control dose formulation was filtered through a 0.2 micron cellulose acetate filter immediately after preparation. The formulations were stored refrigerated during the period of use (<7 days). AL has been shown to be chemically stable in AL/lysine solutions prepared in 0.9% NACl/0.3% purified lysine for at least 8 days when maintained refrigerated.[7]

Artesunate: Dose formulations containing 10, 20, 40, or 80 mg/mL of AS were prepared for use during the LD_{50} phase of the study. For this, a stock formulation containing 133 mg/mL of AS was prepared in 5% sodium bicarbonate. This stock solution was diluted with sterile water to yield a formulation containing 80 mg/mL of AS and also diluted with 0.9 % sterile saline to yield formulations containing 10, 20, or 40 mg/mL of AS.

Dose formulations containing 1.9, 3.75, 7.5, or15 mg/mL of AS were prepared for use during the range-finding phase (Phases 2 and 3). For this, stock formulations containing 120 mg/mL of AS were prepared in 5 % sodium bicarbonate. The stock solutions were diluted, as appropriate, with 0.9 % sterile saline, to yield formulations containing 1.9, 3.75, 7.5, 15, or 30 mg/mL of AS.

The AS vehicle control dose formulation (0 mg/mL of AS) consisted of a solution of 5% sodium bicarbonate in sterile water.

Each AS and corresponding vehicle control dose formulation was filtered through a 0.2 micron cellulose acetate filter immediately after preparation. The formulations were maintained at room temperature and used within 2 hours of preparation. Batty and coworkers have shown that AS is stable for at least 4 hours in bicarbonate/saline solutions maintained at 23°C.[8]

Arteether: The dose formulation of arteether was prepared in sesame oil to contain AE at a concentration of 50 mg/mL. For preparation, a weighed quantity of AE was added to an appropriate volume of sesame oil and the mixture was sonicated and stirred until dissolution of the AE occurred. The AE dose formulation was stored at room temperature.

Previous investigations have shown that AE is stable in sesame oil for at least 1 year when stored at room temperature.[9]

Dose Formulation/Homogeneity Analysis: Each AL/lysine dose formulation prepared during Phases 1, 2, or 3 was analyzed by HPLC at the time of preparation for chemical concentration and homogeneity. In addition, each AL/lysine formulation prepared in Phase 2 was analyzed by HPLC at the end of the dosing period for chemical concentration.

Dose formulations of AS prepared for use during Phase 1 were analyzed by HPLC for chemical concentration and homogeneity immediately after preparation. During Phase 2, dose formulations of AS prepared for use on Days 1, 3, and 7 of the 7-day dosing period were analyzed for chemical concentration and homogeneity. During Phase 3, dose formulations of AS prepared on Days 1 and 7 were analyzed.

2.1.2.3 Experimental Design

Group Assignment

For each study phase, the male and female rats were randomly assigned to dose groups using an Artemis® (Liverpool, Great Britain) computer-generated randomization procedure. For each randomization, the rats were weighed during Week -1, and the mean body weight by sex was used to determine the acceptable weight range. Rats closest to the mean weight by sex were selected for study. Dose group assignments by phase are presented in the tables that follow.

LD_{50} (Phase 1)

Group ID	Formulation	Nominal Dose		Number of Rats	
		Level (mg/kg)	Concentration (mg/mL)	Males	Females
1	AL Vehicle Control	0	0	2	2
2	AL/Lysine	80	16	2	2
3	AL/Lysine	40	8	2	2
4	AL/Lysine	20	4	2	2
5	AS Vehicle Control	0	0	2	2
6	Artesunate	400	80	2	2
7	Artesunate	200	40	2	2
8	Artesunate	100	20	2	2
9	Artesunate	50	10	2	2
10	AL/Lysine	320	64	2	2
11	AL/Lysine	160	32	2	2

Range-Finding (Phase 2)

Group ID	Formulation	Nominal Dose		Number of Rats	
		Level (mg/kg/day)	Concentration (mg/mL)	Males	Females
1	AL Vehicle Control	0	0	3	3
2	AL/Lysine	37.5	6	3	3
3	AL/Lysine	18.8	3	3	3
4	AL/Lysine	9.4	1.5	3	3
5	AL/Lysine	4.7	0.75	3	3
6	AS Vehicle Control	0	0	3	3
7	Artesunate	75	15	3	3
8	Artesunate	37.5	7.5	3	3
9	Artesunate	18.8	3.75	3	3
10	Artesunate	9.4	1.9	3	3
11	Arteether	25	50	3	3

Range-Finding (Phase 3)

Group ID	Formulation	Nominal Dose		Number of Rats	
		Level (mg/kg/day)	Concentration (mg/mL)	Males	Females
12	AL Vehicle Control	0	0	3	3
13	AL/Lysine	80	16	3	3
14	AS Vehicle Control	0	0	3	3
15	Artesunate	150	30	3	3

Dose Procedure

For the LD_{50} phase of the study, rats in Groups 1-9 were dosed on their respective Day 1. As no mortality occurred for rats in the highest AL dose group (Group 2; 80 mg/kg AL/lysine) on or before Day 5 of the study, rats in Groups 10 (160 mg/kg AL/lysine) and 11 (320 mg/kg AL/lysine) were subsequently dosed on their respective Day 1. Each rat received a single iv injection of the designated dose of AL or AS (or the respective vehicle control), as indicated in the preceding tables, via a tail vein; the dose volume administered was 5 mL/kg.

For the dose range-finding phases (Phases 2 and 3), each rat in Groups 1-10 and 14-15 received single daily iv doses, administered via a tail vein, of AL/lysine, AS, or the appropriate vehicle formulation, as indicated in the preceding tables, once daily for 7 consecutive days; rats in Group 11 received single daily im doses of AE, administered into the left or right hind leg, once daily for 7 consecutive days. Rats in Groups 12 and 13 were scheduled to receive single daily iv doses, administered via a tail vein, of AL/lysine or the appropriate vehicle formulation once daily for 7 consecutive days; however, due to necrotic tails, dosing of the rats in Groups 12 and 13 was discontinued after Day 5.

For Phase 2, the dose volume of AL/lysine or the appropriate vehicle formulation administered to rats in Groups 1-5 was 6.25 mL/kg. The dose volume of AS or the appropriate vehicle formulation administered to rats in Groups 6-10 was 5 mL/kg, and the dose volume of AE administered to rats in Group 11 was 0.5 mL/kg. For Phase 3, the dose volume administered to rats in Groups 12-15 was 5 mL/kg.

All doses in all three phases were administered using 3-cc plastic syringes (Becton-Dickinson and Co.; Franklin Lakes, NJ) fitted with 23.5-gauge needles (Sherwood Medical; St. Louis, MO).

Body Weights

For the LD_{50} phase, individual body weights for each rat were obtained during Week –1 (for randomization), on Day 1 (prior to dosing), and on Day 8. For the dose range-finding phases (Phases 2 and 3), individual body weights for each surviving rat were obtained during Week –1 (for randomization), on Days 1-7 prior to dosing, on Day 15, and prior to sacrifice/necropsy on Day 8 (Phase 3, Groups 12 and 13 only) or Day 23.

Clinical Observations

For all phases of the study, the rats were observed once daily during quarantine and twice daily during the study for signs of mortality or moribundity. During the LD_{50} phase, the rats were observed twice daily, morning and afternoon, at least 4 hours apart on Days 1-7, and once on Day 8 prior to sacrifice. These evaluations included an assessment for abnormal posture, activity, level of arousal, and breathing; the site of injection was monitored closely for irritation and/or swelling.

During the dose range-finding phases (Phases 2 and 3), each surviving rat was observed twice daily on Days 1-7, at approximately 1 and 5 hours postdose; twice daily on Days 8-14, morning and afternoon, approximately 4 hours apart; once daily on Days 15-22; and prior to necropsy on

Day 23 for detailed signs of toxicity; the site of injection was monitored closely for irritation and/or swelling or other adverse reactions.

Clinical Pathology

Clinical pathology was not evaluated during the LD_{50} phase. On Day 8 (Phase 3, Groups 12 and 13 only) or Day 15 of the dose range-finding phases (Phase 2 and 3), prior to scheduled necropsy, each rat was anesthetized with CO_2/O_2, and blood samples were obtained from the retro-orbital sinus of each rat into tubes containing EDTA (hematology samples) or no anticoagulant (clinical chemistry samples). Blood samples were used for the following determinations:

	Hematology	
WBC	Total leukocyte count	$10^3/mm^3$
RBC	Erythrocyte count	$10^6/mm^3$
HGB	Hemoglobin	g/dL
HCT	Hematocrit	%
MCV	Mean corpuscular volume	fL
MCH	Mean corpuscular hemoglobin	pg
MCHC	Mean corpuscular hemoglobin concentration	g/dL
PLT	Platelet count	$10^3/mm^3$
RETIC	Reticulocyte count	$10^5/mm^3$
	Differential leukocyte counts (automated)	$10^3/mm^3$
	Clinical Chemistry	
BUN	Blood urea nitrogen	mg/dL
Crea	Creatinine	mg/dL
	BUN/Crea ratio	
ALT	Serum alanine aminotransferase	U/L
AST	Serum aspartate aminotransferase	U/L
ALP	Alkaline phosphatase	U/L
Gluc	Glucose	mg/dL
TP	Total protein	g/dL
Alb	Albumin	g/dL
Glob	Globulin	g/dL
A/G	Albumin/globulin ratio	
Na	Sodium	mEq/L
K	Potassium	mEq/L
Cl	Chloride	mEq/L

Animal Disposition/Necropsy

For the LD_{50} phase, surviving rats were sacrificed on Day 8 by CO_2/O_2 asphyxiation. Carcasses were discarded without evaluation.

For the dose range-finding phases (Phases 2 and 3), with the exception of rats in Groups 12 and 13, all rats in all dose groups were anesthetized on Day 23 with ketamine/xylazine (75 mg/kg/10 mg/kg, administered ip), and sacrificed by exsanguination/perfusion. Because iv dosing was

discontinued early for rats in AL dose groups 12 and 13 due to necrotic tails, rats in these two groups were anesthetized and sacrificed on Day 8, as directed by the Contracting Officer's Representative (COR), following the same procedures. To achieve the perfusion, once each rat was anesthetized, the thorax and pericardium were opened to expose the heart, a needle connected to perfusate was placed in the left ventricle, and the right atrium was opened to effect exsanguination euthanasia. Each rat was perfused with a chilled 0.9% sodium chloride solution containing 1 unit of heparin per mL, for approximately 2 minutes; the heparinized saline perfusion was followed by perfusion with 500-700 mL of Bouin's solution. The brain of each rat was maintained *in situ* for 30-120 minutes prior to dissection. The following tissues were examined at necropsy:

Adrenals (2)
Bone
Cecum
Colon
Duodenum
Epididymis
Esophagus
Eyes (2)
Fallopian tube
Gross lesions
Injection site (tail)
Heart
Ileum
Jejunum
Kidneys (2)
Liver
Lungs and bronchi
Lymph nodes (mesenteric)
Mammary gland (females only)
Marrow (femur)
Ovaries (2)
Pancreas
Pituitary
Prostate
Salivary gland
Sciatic nerve
Seminal vesicle
Skin
Skeletal muscle
Spleen
Stomach
Testes (2)
Thyroid/parathyroid (2)
Thymus
Tongue
Urinary bladder
Uterus (corpus and cervix)
Vagina

The protocol specified that nonbrain tissues were to be saved and fixed only if gross examination revealed abnormalities. For Phase 2 of the study, no gross abnormalities were seen, so no tissues other than brain were retained. For Phase 3 of the study, animals in Group 15 had gross abnormalities of the tail at the injection site, so that tissue was retained and saved in Bouin's fixative.

The brain was removed 90-120 minutes after perfusion and immersed in fresh Bouin's fixative overnight. After 24 hours, the brain was dissected as follows:

- A transverse cut was made at the spino-medullary junction, caudal to the dorsal column nuclei.
- A second transverse cut was made immediately caudal to the inferior colliculi.
- The cerebellum remained attached to this hindbrain block.
- The midbrain and forebrain blocks were stored in 70 % ethanol and then forwarded to the Sponsor for study.

Histopathology

The hindbrain, cerebellum, and other sections of the brain were processed as follows:

Clearing of picric acid (from Bouin's solution): Brains were immersed in 70% ethanol, and the ethanol was changed every 24 hours, until the brains were no longer colored with picric acid.

Dehydration, clearing, and embedding: Each brain was dehydrated in ascending grades of ethyl alcohol and then cleared with xylene. Subsequently, the tissues were embedded in paraffin. Only one brain section was embedded per paraffin block.

Microtomy: Serial transverse sections were cut through the hindbrain at 10-μm increments. The sections were mounted on slides according to the following scheme: Sections #0 and 1 were mounted on first glass slide for hematoxylin and eosin (H&E) staining. Sections #2 and 3 were mounted on another glass slide for K-B staining. Sections #5 and 6 were mounted on another glass slide for staining with the Nissl method (cresyl violett). Sections #20 and 21 were mounted for H&E staining. Sections #22 and 23 were mounted on another microslide for K-B. Sections #24 and 25 were mounted for Nissl (cresyl violett) staining. Thereafter, every 20^{th}-25^{th} section was mounted in this same sequence until the entire hindbrain/cerebellum block had been processed. The remaining serial sections that were cut were retained.

Sections were examined microscopically a board certified pathologist. For the brain tissues, lesions were graded for severity on a five-point scale with 0 as normal and 4 as the most severe. The study pathologist established criteria for each of these grades, and the severity criteria related to the number or percentage of neurons involved. The nuclear groups studied included the vestibular [n. vestibularis medialis; n. vestibularis descendens (spinal)], the reticular formation (n. gigantocellularis; n. pontis centralis caudalis; n. pontis centralis oralis), and the auditory system (n. trapezoidalis; n. olivaris superior). For the nonbrain tissues, a four-step grading system of trace, mild, moderate, or severe was used, when appropriate, to rank the severity of microscopic findings for comparison among groups

Statistical Analyses

No statistical analyses were performed on data generated during the LD_{50} phase. For the dose range-finding phases (Phases 2 and 3), the group mean and standard deviation was calculated for each dose-sex group for body weights and the hematology and clinical chemistry parameters; these data were also subjected to statistical analysis by ANOVA, followed by Dunnett's test. In all cases, the lower limit for statistical significance was defined as $p<0.05$.

2.1.3 Results

2.1.3.1 Results: LD_{50} Phase

Mortality

A summary of the mortality observed during the LD_{50} phase is presented in Table 1. Two of two female rats in the 160 mg/kg AL/lysine dose group and 2/2 male and 2/2 female rats in the 320 mg/kg AL/lysine dose group died on Day 1 within 30 minutes after dosing.

Two of two male and 2/2 female rats in the 400 mg/kg AS dose group were found dead on Day 2.

Clinical Observations

Individual clinical observations recorded during the LD_{50} phase of the study are presented in Table 2. Prostration and/or hypoactivity were observed after dosing on Day 1 for 2/2 males in the 160 mg/kg AL dose group; these clinical signs were transient and were not observed at the second scheduled daily observation period which occurred approximately 4 hours after dosing. Other adverse clinical signs of toxicity noted for rats given AL were related to abnormalities in the tail of the animals. Black or dark discoloration of the tail was observed on Days 2-8 for 1/2 males and 2/2 females in the 80 mg/kg AL dose group and for 2/2 males in the 160 mg/kg AL dose group; in addition, partial loss of the tail occurred on Day 5 for one of the female rats in the 80 mg/kg AL dose group. Necrosis of the tail was also noted on Days 5-8 for 2/2 male rats in the 160 mg/kg AL dose group.

For rats given AS, the only adverse clinical sign noted was ataxia within the first 30 minutes after dosing on Day 1 for 1/2 males and 2/2 females in the 400 mg/kg AS dose group; the ataxia was transient and was not observed at the second scheduled daily clinical observation period which was conducted approximately 4 hours later.

Body Weights

Body weights for individual rats, along with group means and standard deviations, recorded during the LD_{50} phase of the study are presented in Table 3. A reduction in mean body weight gain, compared to the corresponding vehicle control rats, was observed for male and female rats in the 80 mg/kg AL dose group between Days 1 and 8. Body weight loss (5% of mean value) was observed between Day 1 and 8 for male rats in the 160 mg/kg AL dose groups; female rats in the 160 mg/kg AL dose groups and male and female rats in the 320 mg/kg AL dose group died prior to Day 8.

The mean body weight gain between Days 1 and 8 of male and female rats given 50, 100, or 200 mg/kg of AS was similar to that of animals in the corresponding vehicle control group; the male and female rats given 400 mg/kg of AS died prior to the scheduled body weight measurements on Day 8.

2.1.3.2 Results: Dose Range-Finding Phase (Phases 2 and 3)

Mortality

A summary of the mortality that occurred during Phases 2 and 3 is presented in Table 4. No mortality was observed for male and female rats given iv doses of AL of 4.7, 9.4, 18.8, or 37.5 mg/kg/day for 7 consecutive days or 80 mg/kg/day for ≤4 days.

No mortality was observed for male and female rats given iv doses of AS of 9.4, 18.8, 37.5, or 75 mg/kg/day for 7 consecutive days or for male rats given 150 mg/kg/day for 7 consecutive days; 1/3 female rats given 150 mg/kg/day of AS was found dead on Day 6.

No mortality was observed for male or female rats given an im dose of AE of 25 mg/kg/day for 7 consecutive days.

Note: After the completion of the histopathological evaluations of the Phase 3 animals had been completed, it was discovered that, during Phase 3, not all rats in the 80 mg/kg/day AL dose group had received an iv dose for 4 days, as previously reported. It was found that all 3 male and all 3 female rats in the 80 mg/kg/day AL dose group were successfully dosed iv on Days 1 and 2. But it appeared from the raw data that on Days 3, 4, and 5, the 3 male and 2 of the 3 female rats were dosed into the tail but not the tail vein; after the first day of dosing, the tails of the rats given AL became swollen and subsequently turned black making it difficult to see the tail veins. One of the three female rats was successfully dosed iv on Days 1, 2, 4, and 5 but not on Day 3. The COR was contacted as soon as this error was discovered.

Clinical Observations

Clinical observations noted during Phases 2 and 3 are summarized in Table 5. No adverse clinical signs were observed for male or female rats given iv doses of 0, 4.7, 9.4, or 18.8 mg/kg/day of AL for 7 consecutive days. Adverse clinical signs observed for rats given 37.5 mg/kg/day of AL were limited to abnormalities of the tail and included swelling of the tail in one or more male or female rats on multiple days between Days 2 and 13; in addition, a sore or ulcer was observed on the tail of 1/3 male and 1/3 female rats between Days 8-12 or Days 5-16, respectively. For rats given 80 mg/kg/day of AL for ≤4 days, hunched posture was noted for 3/3 males and 3/3 females on one or more days between Days 4 and 8; one of three female rats in this dose group also appeared emaciated on Day 8. Other adverse clinical signs observed for rats given 80 mg/kg/day of AL were restricted to the tail and included: black or dark tail in 3/3 male (Days 3-4) and 1/3 or 2/3 female (Day 1 or Day 2) rats, and tail swelling and necrosis in 3/3 males (Day 5) and 1 or 2/3 females (Days 4 and/or 5 and Day 8). Due to the development of a dark colored or swollen tail, by Day 5 it had become virtually impossible to see a vein in the tail of all animals in the 80 mg/kg/day AL dose group and dosing was discontinued after this day for animals in this dose group and the corresponding vehicle control group.

No adverse clinical signs were observed for male and female rats given iv doses of 0, 9.4, 18.8, or 37.5 mg/kg/day of AS for 7 consecutive days. One of three male rats in the 75 mg/kg/day AS

dose group displayed a swollen tail on Days 9-12. No adverse clinical signs were observed for male rats given 150 mg/kg/day of AS for 7 consecutive days. The female rat in the 150 mg/kg/day AS dose group that was found dead on Day 6 displayed diarrhea, a nasal discharge, and hunched posture for 1 or 2 days preceding death. The other two female rats in the 150 mg/kg/day AS dose group displayed diarrhea, emaciation, a nasal discharge, hunched posture, and wet/skin fur in the abdominal/vulvular region on 2 or more days between Days 3 and 8; in addition, a sore/ulcer was noted on the tail of each of these two rats on Days 17 and 18.

No adverse clinical signs were observed on any day during the study for male or female rats given an im dose of 25 mg/kg/day of AE for 7 consecutive days.

Body Weights

Group mean body weights for animals dosed during Phases 2 and 3 are summarized in Table 6. Male and female rats given 4.7, 9.4, 18.8, or 37.5 mg/kg/day of AL daily for 7 consecutive days gained weight throughout the study and their rate of weight gain was similar to that observed for rats in the corresponding vehicle control group. Body weight loss was observed on multiple days between Day 1 and Day 8 for male and female rats given 80 mg/kg/day of AL for ≤4 days. The greatest decrease in body weight was observed on Day 5 for male rats and on Day 6 for female rats where the mean body weights of the animals were 87.9% and 82.8%, respectively, of the corresponding Day 1 mean body weight.

Male and female rats given 9.4, 18.8, or 37.5 mg/kg/day of AS, daily for 7 consecutive days, gained comparable amounts of body weight during the study to the male and female rats in the corresponding vehicle control groups. Decreased body weight gain, compared to the corresponding vehicle control rats, and/or body weight loss was observed during the dosing period for male and female rats in the 75 and 150 mg/kg/day AS dose groups. The greatest body weight loss was observed on Day 5 for the female rats in the 150 mg/kg/day AS dose group, where the mean body weight of the animals was 89.4% of Day 1.

Male and female rats given 25 mg/kg/day of AE, daily for 7 consecutive days, gained weight throughout the study and their rate of body weight gain was comparable to that of the animals the AL and AS vehicle control groups dosed during Phase 2.

Hematology

Group mean hematology values are summarized in Table 7. Group mean values were compared to the corresponding group mean vehicle control values; group mean values for rats in the arteether dose group were compared to the AS vehicle control group as there was no comparable vehicle control group. Individual values from rats in all AL, AS, and AE dose groups were also compared to the range of values that was observed for rats in all the vehicle control groups as no appreciable differences in clinical pathology parameters were observed between the different vehicle control groups. Statistical significance was considered; however, the small group size limited the value of these findings. Differences in group means were considered biologically relevant if they were greater than those differences expected to be due to analytical or interindividual variability.

Artelinate

Group mean WBC counts that were observed on Day 8 for male and female rats in the 80 mg/kg/day AL dose group were mildly increased with values that were 2.0- and 2.1-fold greater than the values observed for rats in the vehicle control group. Mild (2.0- to 3.9-fold) to moderate (4.0- to 5.9-fold) increases in the group mean neutrophil counts were observed for male and female rats in the 80 mg/kg/day AL dose group on Day 15 with values that were 3.8- and 5.1-fold, respectively, greater than the values observed for rats in the corresponding vehicle control group. Increased group mean monocyte counts were also observed for male and female rats in the 80 mg/kg/day AL dose group with values that were 2.3- and 4.7-fold greater than the values observed for rats in the corresponding vehicle control group. Minimal increases in lymphocyte counts were also observed for male and female rats in the 80 mg/kg/day AL dose group with values that were 1.6- and 1.7-fold greater than the values observed for rats in the vehicle control groups.

The group mean RBC, HGB, and HCT values that were observed for male and female rats in the 80 mg/kg/day AL dose group on Day 8 were decreased; group mean RBC values were 84% and 79%, respectively, of the values observed for rats in the corresponding vehicle control group.

A trend for minimal increases (1.5- to 1.9- fold greater than vehicle control values) in the group mean reticulocyte percent or counts was observed for male and female rats in the 9.4, 18.8, and 37.7 mg/kg/day AL dose groups on Day 15 and for male rats in the 80 mg/kg/day AL dose group on Day 8. For both male and female rats, at least 2/3 rats in each of these dose groups were observed to have reticulocyte count or percent values that were greater than the maximal values observed for rats in all vehicle control groups. While the predominance of individual rats with reticulocyte values outside the range of values observed for vehicle control rats was consistent with a drug-related response, the lack of appreciable changes in erythrocyte parameters suggested that the change was of limited toxicological relevance.

Clinical observations of tail swelling and tail necrosis that were noted for rats in the 80 mg/kg/day AL dose group were consistent with findings of leukocytosis, neutrophilia, and monocytosis. While decreases in RBC, HGB, and HCT values may occur secondarily to weight loss or decreased weight gain in rats, the combination of decreased erythrocyte values and the presence of mild to moderate increases in group mean reticulocyte values in male rats and both increased and decreased reticulocyte values in female rats were more consistent with a drug-related effect on hematopoiesis.

Artesunate

No biologically relevant differences in the group mean WBC counts were observed for rats in the AS dose groups; however, an increased individual WBC count (greater than the maximum value observed for rats in all vehicle control groups) was observed in 1/2 female rats in the 150 mg/kg/day AS dose group on Day 15. Increased group mean neutrophil counts were observed for female rats in the 75 and 150 mg/kg/day AS dose groups on Day 15, with values that were 2.1- and 3.8-fold greater than the values observed for rats in the

vehicle control group. Monocyte counts were increased in 1/2 male rats in the 150 mg/kg/day AS dose group.

A decreased group mean RBC value was also observed for female rats in the 150 mg/kg/day AS dose group with a value that was 79% of the value observed for rats in the vehicle control group. The group mean MCV value that was observed for female rats in the 150 mg/kg/day AS dose group was increased, with a value that was 108% of the value observed for rats in the vehicle control group.

Administration of 150 mg/kg/day of AS for 7 consecutive days was associated with mild (2.0- to 3.9-fold) to moderate (4.0- to 5.9-fold) increases in group mean reticulocyte percent and counts on Day 15 in female rats, with values that were 4.2- and 3.4-fold greater than the values observed for rats in the corresponding vehicle control group. Minimal increases (1.8- and 1.6-fold greater than vehicle control values) in group mean reticulocyte percent or counts that were observed for male rats in the 18.8 mg/kg/day AS dose group were considered to be not clearly compound related or not of toxicological relevance due to the lack of a dose-relationship, the minimal magnitude of the change, and the lack of changes in RBC, HGB, and HCT.

Clinical observations of tail swelling and tail necrosis that were noted for rats in the 150 mg/kg/day AS dose group were consistent with findings of neutrophilia and monocytosis. While decreases in RBC, HGB, and HCT values may occur secondarily to weight loss or decreased weight gain in rats, the combination of decreased erythrocyte values, increased MCV, and the presence of mild to moderate increases in group mean reticulocyte values in female rats in the 150 mg/kg/day AS dose group were consistent with a drug-related effect on hematopoiesis.

Arteether

Hematology changes associated with im administration of 25 mg/kg/day of AE for 7 consecutive days were limited to minimal increases in group mean reticulocyte percents and counts observed in male rats on Day 15, with values that were 1.9- and 1.8-fold greater than the values observed for rats in the corresponding vehicle control group. All rats in this dose group were observed to have individual reticulocyte percents and counts that were greater than the maximum value that was observed for rats in the vehicle control group. Female rats in the 25 mg/kg/day AE dose group were also observed to have slight increases in group mean reticulocyte percent and count; however, the differences were not considered biologically relevant due to the minimal magnitude of the responses.

Clinical Chemistry

Group mean clinical chemistry values are summarized in Table 8. Group mean values were compared to the corresponding group mean vehicle control values; group mean values for rats in the arteether dose group were compared to the AS vehicle control group as there was no comparable vehicle control group. Individual values from rats in all AL, AS, and AE dose groups were also compared to the range of values that was observed for rats in all the vehicle control groups as no appreciable differences in clinical pathology parameters were observed between the different vehicle control groups. Statistical significance was

considered; however, the small group size limited the value of these findings. Differences in group means were considered biologically relevant if they were greater than those differences expected to be due to analytical or interindividual variability.

Artelinate

The group mean total protein value observed on Day 8 for female rats in the 80 mg/kg/day AL dose group was decreased, with a value that was 93% of the value observed for rats in the vehicle control group. Three of three rats in this 80 mg/kg/day dose group were observed to have total protein values that were less than the range of values observed for rats in all of the control groups. The group mean albumin values observed on Day 8 for male and female rats in the 80 mg/kg/day AL dose group were decreased, with values that were 77% and 74%, respectively, of the values observed for rats in the corresponding vehicle control groups. All rats in this dose group were observed to have albumin values that were less than the minimum value observed for rats from all of the vehicle control groups. Increases in the group mean globulin value were observed for male and female rats in the 80 mg/kg/day AL dose group on Day 8 with values that were 1.4- and 1.3-fold, respectively, greater than the values observed for rats in the vehicle control group. Decreases in the group mean A/G ratios were also observed for male and female rats in the 80 mg/kg/day AL dose group on Day 8 with values that were 58% and 57%, respectively, of the value observed for rats in the vehicle control group.

The pattern of decreases in albumin and A/G ratios and increases in globulin values was consistent with changes associated with inflammation and was consistent with clinical observations of tail swelling and necrosis that were noted for rats in the 80 mg/kg/day AL dose group. The decreases in group mean total protein, albumin, and A/G ratios and increases in group mean globulin values were considered to be biologically relevant and drug related as the pattern was consistently observed for rats in the 80 mg/kg/day dose group.

The group mean BUN and creatinine values observed for female rats in the 80 mg/kg/day AL dose group on Day 8 were increased, with values that were 140% and 138%, respectively, of the values observed for rats in the vehicle control group. On review of individual data, 1/3 and 2/3 of the rats in this dose group were observed to have BUN or creatinine values, respectively, that were greater than the maximum values observed for rats in all vehicle control groups.

Other statistically significant findings including; increases in group mean glucose (female, 4.7 mg/kg/day of AL, Day 15) and chloride (female, 4.7 or 18.8 mg/kg/day of AL, Day 15) and decreases in ALT (9.4 mg/kg/day of AL, Day 15), were not considered to be biologically relevant or drug related due to the minimal magnitude of the responses, the lack of a dose-relationship, and the presence of data for individual animals that were generally comparable to data for the vehicle control animals.

Artesunate

The group mean albumin value observed for female rats in the 150 mg/kg/day AS dose group on Day 15 was decreased with a value that was 76% of the value observed for rats in

the corresponding vehicle control group. All female rats in this dose group were observed to have albumin values that were less than the minimum value observed for rats from all of the vehicle control groups. Increases in the group mean globulin values were observed for female rats in the same dose group, with a group mean globulin value that was 1.6-fold greater than the value observed for rats in the vehicle control group. A decrease in the group mean A/G ratio was also observed for female rats in the 150 mg/kg/day AS dose group on Day 15, with a value that was 49% of the value that was observed for rats in the corresponding vehicle control group.

The pattern of decreases in albumin and A/G ratios and increases in globulin values that were observed for female rats in the 150 mg/kg/day AS dose group was consistent with changes associated with inflammation. The decreases in group mean total protein, albumin, and A/G ratios and increases in group mean globulin values were considered to be drug related and consistent with clinical observations of tail sores/ulcers and diarrhea.

Arteether
No clinical chemistry changes were associated with im administration of 25 mg/kg/day of AE to rats for 7 consecutive days.

Macroscopic and Microscopic Pathology
There were no macroscopic or microscopic lesions in the hindbrain of rats that were related to treatment with AL at doses up to 80 mg/kg/day or to treatment with AS at doses up to 150 mg/kg/day. The hindbrain of all animals in the AL or AS dose groups that were examined was within normal limits.

For animals in the 25 mg/kg/day AE dose group, no lesions were noted in the hindbrains of male rats but lesions were observed in 1/3 female rats. The degenerative lesions that were noted in the female rats consisted of neuronal degeneration of 2 to 4 cells per section in the trapezoid nucleus.

2.1.4 Discussion

The results of this study indicated that one of the significant clinical signs of toxicity produced by iv administered AL was a black and/or dark discoloration of the tail, which in some instances was accompanied by necrosis. In that the iv doses were administered into a tail vein, the occurrence of tail discoloration/necrosis indicated that AL had a direct adverse effect on the vein and/or the surrounding tissue into which the dose was administered. Tail discoloration/necrosis was observed for rats given either single or multiple doses of AL. The occurrence of tail vein necrosis appeared to be dose dependent, suggesting that the venotoxicity produced by AL may have been a function of the concentration of AL in the dose formulation. Adverse effects on the tail vein/tail tissue were not observed for rats given single or multiple iv doses of AS.

Although the rats in the 80 mg/kg/day AL dose group received only 4 or less iv doses (instead of the protocol-specified 7 daily doses), clinical pathological changes were observed on Day 8 for rats in this dose group. These changes, which were considered to be of possible toxicological significance, included increases in group mean WBC values, reticulocyte percents or counts, neutrophil counts, lymphocyte counts, monocyte counts, platelet counts, and globulin values, and

decreases in RBC, HGB, and HCT, total protein, albumin, and A/G ratio values. The increases in RBC, HGB, and HCT values, in combination with the presence of mild to moderate increases in reticulocyte values, suggested that AL may have effected hematopoiesis. The decreases in albumin and A/G ratios and increases in globulin values, as well the observed leukocytosis, neutrophilia, and monocytosis, were consistent with changes associated with inflammation and correlated with the tail swelling and tail necrosis observed for rats in the 80 mg/kg/day AL dose group. Clinical pathological changes observed on Day 15 for female rats given 150 mg/kg/day of AS for 7 consecutive days were also consistent with an effect of AS on hematopoiesis. In contrast, a possible hematopoietic effect was not observed following 7-day im administration of AE to rats.

A major focus of this study was to investigate the occurrence of histopathological lesions in the brains of rats given iv doses of AL or AS. Previous investigations have shown that AE produced dose-dependent brainstem neurotoxicity in rats and monkeys, which was characterized by lesions in brainstem nuclei in the reticular formation, the vestibular system, and the auditory system.[11,12] In the current study, no evidence was obtained for the presence of histopathological lesions in the brains of rats given up to 150 mg/kg/day of AS for 7 consecutive days. In addition, no evidence was obtained for the occurrence of histopathological lesions in the hindbrains of rats given ≤37.5 mg/kg/day of AL for 7 consecutive days; due to the problematic dosing, no conclusions could be made regarding the possible neuropathy produced by multiple dose administration of higher doses of AL.

A decision regarding whether additional attempts will be made on this study to dose rats iv with AL is pending the outcome of a decision-making meeting to be held at WRAIR in early October, 2002.

3.0 KEY RESEARCH ACCOMPLISHMENTS

Key research accomplishments during the past year of the contract included:

- Determination that the maximum tolerated dose of AL in rats given a single iv dose, formulated as lysine salt, was 80 mg/kg.

- Determination that the maximum tolerated dose of AS in rats given a single iv dose was 200 mg/kg.

- Determination that for rats given multiple iv doses of AL, the maximum tolerated dose was ≥37.5 mg/kg/day of AL, when given daily for 7 consecutive days (total dose: ≥262.5 mg/kg)

- Determination that for rats given multiple iv doses of AS, the maximum tolerated dose was ≥75 mg/kg/day of AS, when given daily for 7 days (total dose: ≥525 mg/kg).

- Determination that iv injection of AL, but not AS, into the tail vein of rats produced an apparent venotoxicity characterized by black or dark discoloration, swelling, and/or necrosis of the tail.

- Determination that clinical pathological changes observed for rats given a daily dose of 80 mg/kg/day of AL for ≤4 days and for rats given a daily iv dose of 150 mg/kg/day of AS for 7 consecutive days, but not for rats given a daily im dose of 25 mg/kg/day of AE for 7 days, were consistent with compound-related effects on hematopoiesis.

- Confirmation that histopathological lesions were produced in the brainstem of rats given a daily im dose of 25 mg/kg/day of AE for 7 consecutive days.

- Determination that no histopathological lesions were produced in the brainstem of rats given a daily iv dose of AL of ≤37.5 mg/kg/day for 7 consecutive days.

- Determination that no histopatholical lesions were produced in the brainstem of rats given a daily iv dose of AS of ≤150 mg/kg/day for 7 consecutive days.

4.0 REPORTABLE OUTCOMES

To date, there have been no reportable outcomes for work completed during the past year of the contract.

5.0 CONCLUSIONS

For rats given single iv doses, mortality was observed at AL doses of ≥160 mg/kg and at an AS dose of 400 mg/kg. Thus, the maximum tolerated dose of AL for rats given a single iv dose was 80 mg/kg and the maximum tolerated dose of AS for rats given a single iv dose was 200 mg/kg.

Following 7 consecutive days of iv dose administration, no mortality was observed for male and female rats given ≤37.5 mg/kg/day of AL (total dose: ≤262.5 mg/kg) or ≤75 mg/kg/day of AS (total dose: ≤525 mg/kg). Due to the difficulty encountered during the iv administration of AL, no conclusions could be drawn relative to the lethality produced by higher multiple iv doses of AL.

The results of this study indicated that one of the significant clinical signs of toxicity produced by iv administered AL was a black and/or dark discoloration of the tail, which in some instances was accompanied by necrosis. In that the iv doses were administered into a tail vein, the occurrence of tail discoloration/necrosis indicated that AL had a direct adverse effect on the vein and/or the surrounding tissue into which the dose was administered. Tail discoloration/necrosis was observed for rats given either single or multiple doses of AL. The occurrence of tail vein necrosis appeared to be dose dependent, suggesting that the venotoxicity produced by AL may have been a function of the concentration of AL in the individual dose formulations that were

administered. Adverse effects on the tail vein/tail tissue were not observed for rats given single or multiple iv doses of AS.

Additional clinical signs of toxicity observed for rats given multiple doses of AL, and also for rats given multiple doses of AS or AE, included clinical pathological changes. Although rats in the 80 mg/kg/day AL dose group received only ≤4 iv doses of AL, clinical pathological changes were noted animals in this dose group. The changes that were observed on Day 8 for rats in this dose group and which were considered to be of possible toxicological significance included increases in group mean WBC values, reticulocyte percents or counts, neutrophil counts, lymphocyte counts, monocyte counts, platelet counts, and globulin values, and decreases in RBC, HGB, and HCT, total protein, albumin, and A/G ratio values. The increases in RBC, HGB, and HCT values, in combination with the presence of mild to moderate increases in reticulocyte values, suggested that AL may have effected hematopoiesis. The decreases in albumin and A/G ratios and increases in globulin values, as well the observed leukocytosis, neutrophilia, and monocytosis, were consistent with changes associated with inflammation and correlated with the tail swelling and tail necrosis observed for rats in the 80 mg/kg/day AL dose group. Clinical pathological changes observed on Day 15 for female rats given 150 mg/kg/day of AS for 7 consecutive days were also consistent with an effect of AS on hematopoiesis. In contrast, a possible hematopoietic effect was not observed following 7-day im administration of AE to rats; clinical pathological changes observed for rats in the AE dose group were limited to minimal increases in group mean reticulocyte percents and counts.

No evidence was obtained for the presence of histopathological lesions in the hindbrains of rats given doses of ≤150 mg/kg/day of AS for 7 consecutive days. In addition, no evidence was obtained for the occurrence of histopathological lesions in the hindbrains of rats given ≤37.5 mg/kg/day of AL for 7 consecutive days; due to the problematic dosing, no conclusions could be made regarding the possible neuropathy produced by multiple dose administration of higher doses of AL. Histopathological lesions were observed, however, for rats given daily im doses of 25 mg/kg/day of AE for 7 consecutive days.

6.0 REFERENCES

1. Oduola, AMJ; Milhous, WK; Salako, LA; Walker, O; Desjardins, RE. (1987). Reduced in-vitro susceptibility to mefloquine in West African isolates of *Plasmodium falciparum*. *Lancet* **Dec 5**:1304-5.

2. Klayman, DL. (1985). Qinghaosu (artemisinin): an antimalarial drug from China. *Science* **228**:1049-1055.

3. Brossi, A; Venugopalan, B; Gerpe, LD; Yeh, HJC; Flippen-Anderson, JL; Buchs, P; Luo, XD; Milhous, W; Peters, W. (1988). Arteether, a new antimalarial drug: Synthesis and antimalarial properties. *J. Med. Chem.* **31**:645-650.

4. Lin, AJ; Klayman, DL; Milhous, WK. (1987). Antimalarial activity of new water-soluble dihydroartemisinin derivatives. *J. Med. Chem.* **30**:2147-2150.

5. Package Insert, Artesunate for Injection, Atlantic Pharmaceutical Co, Bangkok

6. Guide for the Care and Use of Laboratory Animals (1996). Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council; National Academy Press; Washington, D.C.

7. Noker, PE (2002). Study of injectable artelinic acid in dogs. Final report for Task Order SR00-1 under Contract DAMD17-98-D-0032.

8. Batty, KT; Ilett, KF: Davis, T, and Davis, ME (1995). Chemical stability of artesunate injection and proposal for its administration by intravenous infusion. *J. Pharm. Pharmacol.* 48**: 22-26.**

9. Lach, JL; Douglas, DR; Flanagan, R; Matheson, LE, Jr. (1987) Formulation and production of beta-arteether injection in sesame oil (Lot WRA-26-11127) and sesame oil diluent/placebo (WRA-25-11127) injection. University of Iowa. Report to USAMRDC under Contract No. DAMD17-85-C-5003, 1987 December 15.

Table 1

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Summary of Mortality: Phase 1, LD_{50} Phase, Males

Dose Group	Formulation	Dose Level (mg/kg/day)	Day of Study									Number Dead/ Number Dosed
			1	2	3	4	5	6	7	8	9	
1	AL Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/2
2	AL/Lysine	80	0	0	0	0	0	0	0	0	a	0/2
3	AL/Lysine	40	0	0	0	0	0	0	0	0	a	0/2
4	AL/Lysine	20	0	0	0	0	0	0	0	0	a	0/2
5	AS Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/2
6	Artesunate	400	0	2								2/2
7	Artesunate	200	0	0	0	0	0	0	0	0	a	0/2
8	Artesunate	100	0	0	0	0	0	0	0	0	a	0/2
9	Artesunate	50	0	0	0	0	0	0	0	0	a	0/2
10	AL/Lysine	320	2									2/2
11	AL/Lysine	160	0	0	0	0	0	0	0	a		0/2

[a] Scheduled sacrifice; scheduled sacrifices are not tabulated, table includes unscheduled deaths only.

Table 1 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Summary of Mortality: Phase 1, LD_{50} Phase, Females

Dose Group	Formulation	Dose Level (mg/kg/day)	Day of Death									Number Dead/ Number Dosed
			1	2	3	4	5	6	7	8	9	
1	AL Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/2
2	AL/Lysine	80	0	0	0	0	0	0	0	0	a	0/2
3	AL/Lysine	40	0	0	0	0	0	0	0	0	a	0/2
4	AL/Lysine	20	0	0	0	0	0	0	0	0	a	0/2
5	AS Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/2
6	Artesunate	400	0	2								2/2
7	Artesunate	200	0	0	0	0	0	0	0	0	a	0/2
8	Artesunate	100	0	0	0	0	0	0	0	0	a	0/2
9	Artesunate	50	0	0	0	0	0	0	0	0	a	0/2
10	AL/Lysine	320	2									2/2
11	AL/Lysine	160	2									2/2

[a] Scheduled sacrifice; scheduled sacrifices are not tabulated, table includes unscheduled deaths only.

Table 2

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Clinical Observation Summary

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)	
1M	1	Unremarkable	(1 - 8)	
		Scheduled sacrifice	(9 - 9)	
	2	Unremarkable	(1 - 8)	
		Scheduled sacrifice	(9 - 9)	
2M	3	Unremarkable	(1 - 1)	(6 - 8)
		Discoloration	(2 - 5)	
		Scheduled sacrifice	(9 - 9)	
	4	Unremarkable	(1 - 8)	
		Scheduled sacrifice	(9 - 9)	
3M	5	Unremarkable	(1 - 8)	
		Scheduled sacrifice	(9 - 9)	
	6	Unremarkable	(1 - 8)	
		Scheduled sacrifice	(9 - 9)	

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 2 (continued)
Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Clinical Observation Summary

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
4M	7	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	8	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
5M	9	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	10	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
6M	11	Unremarkable	(1 - 1)
		Ataxia	(1 - 1)
		Found dead	(2 - 2)
	12	Unremarkable	(1 - 1)
		Found dead	(2 - 2)

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 2 (continued)
Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Clinical Observation Summary

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
7M	13	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	14	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
8M	15	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	16	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
9M	17	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	18	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 2 (continued)
Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Clinical Observation Summary

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
10M	19	Found dead	(1 - 1)
	20	Found dead	(1 - 1)
11M	21	Sore/ulcer	(4 - 8)
		Discoloration	(1 - 8)
		Hypoactive	(1 - 1)
		Prostrate	(1 - 1)
		Necrosis	(6 - 8)
		Scheduled sacrifice	(8 - 8)
	22	Sore/ulcer	(4 - 8)
		Ataxia	(1 - 1)
		Discoloration	(1 - 8)
		Hypoactive	(1 - 1)
		Necrosis	(6 - 8)
		Scheduled sacrifice	(8 - 8)

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 2 (continued)
Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Clinical Observation Summary

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
1F	23	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	24	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
2F	25	Unremarkable	(1 - 1)
		Discoloration	(2 - 8)
		Missing anatomy	(5 - 8)
		Scheduled sacrifice	(9 - 9)
	26	Unremarkable	(1 - 1)
		Discoloration	(2 - 8)
		Scheduled sacrifice	(9 - 9)
3F	27	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	28	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 2 (continued)
Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Clinical Observation Summary

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
4F	29	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	30	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
5F	31	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	32	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
6F	33	Unremarkable	(1 - 1)
		Ataxia	(1 - 1)
		Found dead	(2 - 2)
	34	Unremarkable	(1 - 1)
		Ataxia	(1 - 1)
		Found dead	(2 - 2)

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 2 (continued)
Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Clinical Observation Summary

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
7F	35	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	36	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
8F	37	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	38	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
9F	39	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)
	40	Unremarkable	(1 - 8)
		Scheduled sacrifice	(9 - 9)

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 2 (continued)
Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Clinical Observation Summary

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
10F	41	Found dead	(1 - 1)
	42	Found dead	(1 - 1)

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
11F	43	Found dead	(1 - 1)
	44	Found dead	(1 - 1)

Comments

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 3

Dose-Range Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Body Weight Summary: Males

Bodyweights (grams)

Group Sex		Day numbers relative to Start Date				
		-7	-5	-2	1	8
1M	Mean	.	.	209.45	228.30	280.95
	S.D.	.	.	5.87	2.83	12.09
	N	0	0	2	2	2
2M	Mean	.	.	210.25	227.45	261.75
	S.D.	.	.	2.90	6.43	19.87
	N	0	0	2	2	2
3M	Mean	.	.	209.95	228.50	283.40
	S.D.	.	.	4.60	8.34	12.45
	N	0	0	2	2	2
4M	Mean	.	.	210.00	229.10	275.80
	S.D.	.	.	0.85	1.84	11.46
	N	0	0	2	2	2
5M	Mean	.	.	210.15	224.60	275.40
	S.D.	.	.	9.26	9.19	16.69
	N	0	0	2	2	2
6M	Mean	.	.	209.15	228.15	.
	S.D.	.	.	6.43	10.68	.
	N	0	0	2	2	0

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 3 (continued)

Dose-Range Study of Injectable Artelinate and Artesunate in Rats (Phase 1: LD_{50})

Body Weight Summary: Males

Bodyweights (grams)

Group	Sex	Day numbers relative to Start Date				
		-7	-5	-2	1	8
7M	Mean	.	.	207.00	223.85	273.35
	S.D.	.	.	4.38	4.74	11.67
	N	0	0	2	2	2
8M	Mean	.	.	211.50	230.15	278.60
	S.D.	.	.	2.97	5.30	9.48
	N	0	0	2	2	2
9M	Mean	.	.	211.75	241.90	307.30
	S.D.	.	.	4.60	2.97	11.31
	N	0	0	2	2	2
10M	Mean	209.00	225.65	.	265.60**	.
	S.D.	6.22	4.03	.	1.13	.
	N	2	2	0	2	0
11M	Mean	215.20	229.40	.	281.85**	268.40
	S.D.	8.06	4.24	.	17.89	30.69
	N	2	2	0	2	2

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 3 (continued)

Dose-Range Study of Injectable Artelinate and Artesunate in Rats (Phase 1)

Body Weight Summary: Females

Group Sex		Bodyweights (grams) Day numbers relative to Start Date -7	-5	-2	1	8
1F	Mean	.	.	187.50	197.90	214.65
	S.D.	.	.	5.09	10.75	6.01
	N	0	0	2	2	2
2F	Mean	.	.	188.35	194.90	173.15
	S.D.	.	.	5.59	3.82	39.53
	N	0	0	2	2	2
3F	Mean	.	.	186.70	192.00	202.60
	S.D.	.	.	5.37	4.24	1.56
	N	0	0	2	2	2
4F	Mean	.	.	184.95	191.15	207.80
	S.D.	.	.	3.75	3.18	6.65
	N	0	0	2	2	2
5F	Mean	.	.	186.75	194.15	201.45
	S.D.	.	.	3.32	2.05	5.59
	N	0	0	2	2	2

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 3 (continued)

Dose-Range Study of Injectable Artelinate and Artesunate in Rats (Phase 1)

Body Weight Summary: Females

Bodyweights (grams)

Group Sex		Day numbers relative to Start Date -7	-5	-2	1	8
6F	Mean	.	.	183.50	189.80	.
	S.D.	.	.	2.83	8.49	.
	N	0	0	2	2	0
7F	Mean	.	.	185.35	190.25	197.20
	S.D.	.	.	7.57	9.97	7.21
	N	0	0	2	2	2
8F	Mean	.	.	185.10	187.80	199.50
	S.D.	.	.	2.26	3.11	12.59
	N	0	0	2	2	2
9F	Mean	.	.	186.10	193.25	212.45
	S.D.	.	.	5.23	7.42	3.89
	N	0	0	2	2	2

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 3 (continued)

Dose-Range Study of Injectable Artelinate and Artesunate in Rats (Phase 1)

Body Weight Summary: Females

Bodyweights (grams)

Group Sex		Day numbers relative to Start Date				
		-7	-5	-2	1	8
10F	Mean	186.30	189.30	.	211.70	.
	S.D.	8.34	13.29	.	14.71	.
	N	2	2	0	2	0
11F	Mean	185.75	194.70	.	214.25	.
	S.D.	0.64	2.97	.	3.18	.
	N	2	2	0	2	0

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01

Nominal Dose: Group 1 - AL-0 mg/kg Group 2 - AL-80 mg/kg Group 3 - AL-40 mg/kg Group 4 - AL-20 mg/kg
Group 5 - AS-0 mg/kg Group 6 - AS-400 mg/kg Group 7 - AS-200 mg/kg Group 8 - AS-100 mg/kg
Group 9 - AS-50 mg/kg Group 10 - AL-320 mg/kg Group 11 - Al-160 mg/kg

Table 4

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Summary of Mortality: Range-Finding Toxicity Phase 2, Males

Dose Group	Formulation	Dose Level (mg/kg/day)	Day of Study									Number Dead/ Number Dosed
			1	2	3	4	5	6	7	8-22	23	
1	AL Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/3
2	AL/Lysine	37.5	0	0	0	0	0	0	0	0	a	0/3
3	AL/Lysine	18.8	0	0	0	0	0	0	0	0	a	0/3
4	AL/Lysine	9.4	0	0	0	0	0	0	0	0	a	0/3
5	AL/Lysine	34.7	0	0	0	0	0	0	0	0	a	0/3
6	AS Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/3
7	Artesunate	75	0	0	0	0	0	0	0	0	a	0/3
8	Artesunate	37.5	0	0	0	0	0	0	0	0	a	0/3
9	Artesunate	18.8	0	0	0	0	0	0	0	0	a	0/3
10	AL/Lysine	9.4	0	0	0	0	0	0	0	0	a	0/3
11	Arteether	25	0	0	0	0	0	0	0	0	a	0/3

[a] Scheduled sacrifice; only unscheduled sacrifices are included as mortality. Due to necrosis of the tail observed for rats in Group 12 which prevented dosing beyond Day 5 for animals in this group, animals in Groups 12 and 13 were sacrificed on Day 8 instead of Day 23.

Table 4 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Summary of Mortality: Range-Finding Toxicity Phase 2, Females

Dose Group	Formulation	Dose Level (mg/kg/day)	Day of Study									Number Dead/ Number Dosed
			1	2	3	4	5	6	7	8-22	23	
1	AL Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/3
2	AL/Lysine	37.5	0	0	0	0	0	0	0	0	a	0/3
3	AL/Lysine	18.8	0	0	0	0	0	0	0	0	a	0/3
4	AL/Lysine	9.4	0	0	0	0	0	0	0	0	a	0/3
5	AL/Lysine	4.7	0	0	0	0	0	0	0	0	a	0/3
6	AS Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/3
7	Artesunate	75	0	0	0	0	0	0	0	0	a	0/3
8	Artesunate	37.5	0	0	0	0	0	0	0	0	a	0/3
9	Artesunate	18.8	0	0	0	0	0	0	0	0	a	0/3
10	Artesunate	9.4	0	0	0	0	0	0	0	0	a	0/3
11	Arteether	25	0	0	0	0	0	0	0	0	a	0/3

[a] Scheduled sacrifice; only unscheduled sacrifices are included as mortality. Due to necrosis of the tail observed for rats in Group 12 which prevented dosing beyond Day 5 for animals in this group, animals in Groups 12 and 13 were sacrificed on Day 8 instead of Day 23.

Table 4 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Summary of Mortality: Range-Finding Toxicity Phase 3, Males

Dose Group	Formulation	Dose Level (mg/kg/day)	Day of Study									Number Dead/ Number Dosed
			1	2	3	4	5	6	7	8	9-23	
12	AL Vehicle Control	0	0	0	0	0	0	0	0	a		0/3
13	AL/Lysine	80	0	0	0	0	0	0	0	a		0/3
14	AS Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/3
15	AS	150	0	0	0	0	0	0	0	0	a	0/3

Summary of Mortality: Range-Finding Toxicity Phase 3, Females

Dose Group	Formulation	Dose Level (mg/kg/day)	Day of Study									Number Dead/ Number Dosed
			1	2	3	4	5	6	7	8	9-23	
12	AL Vehicle Control	0	0	0	0	0	0	0	0	a		0/3
13	AL/Lysine	80	0	0	0	0	0	0	0	a		0/3
14	AS Vehicle Control	0	0	0	0	0	0	0	0	0	a	0/3
15	AS	150	0	0	0	0	0	1	0	0	a	1/3

[a] Scheduled sacrifice; only unscheduled sacrifices are included as mortality. Due to necrosis of the tail observed for rats in Group 12 which prevented dosing beyond Day 5 for animals in this group, animals in Groups 12 and 13 were sacrificed on Day 8 instead of Day 23.

Table 5

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Males

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)	
1M	51	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
	52	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
	53	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
2M	54	Unremarkable	(1 - 5)	(14 - 23)
		Swelling	(6 - 13)	
		Scheduled sacrifice	(23 - 23)	
	55	Unremarkable	(1 - 7)	(14 - 23)
		Swelling	(8 - 13)	
		Scheduled sacrifice	(23 - 23)	
	56	Unremarkable	(1 - 2)	(20 - 23)
		Sore/ulcer	(14 - 19)	
		Swelling	(3 - 13)	
		Scheduled sacrifice	(23 - 23)	

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Males

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
3M	57	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	58	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	59	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
4m	60	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	61	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	62	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Males

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
5M	63	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	64	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	65	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
6M	66	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	67	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	68	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Males

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)	
7M	69	Unremarkable	(1 - 8)	(13 - 23)
		Swelling	(9 - 12)	
		Scheduled sacrifice	(23 - 23)	
	70	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
	71	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
8M	72	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
	73	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
	74	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Males

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
9M	75	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	76	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	77	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
10M	78	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	79	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	80	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Males

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
11M	81	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	82	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	83	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Females

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)	
1F	84	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
	85	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
	86	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
2F	87	Unremarkable	(1 - 4)	(12 - 23)
		Swelling	(5 - 11)	
		Scheduled sacrifice	(23 - 23)	
	88	Unremarkable	(1 - 23)	
		Scheduled sacrifice	(23 - 23)	
	89	Unremarkable	(1 - 1)	(17 - 23)
		Sore/ulcer	(5 - 16)	
		Swelling	(2 - 11)	
		Scheduled sacrifice	(23 - 23)	

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Females

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
3F	90	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	91	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	92	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
4F	93	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	94	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	95	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Females

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
5F	96	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	97	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	98	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
6F	99	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	100	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	101	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Females

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
7F	102	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	103	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	104	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
8F	105	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	106	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	107	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Females

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
9F	108	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	109	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	110	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
10F	111	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	112	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	113	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 5 (continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunatte in Rats (Phase 2)

Clinical Observation Summary: Females

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
11F	114	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	115	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)
	116	Unremarkable	(1 - 23)
		Scheduled sacrifice	(23 - 23)

Nominal Dose: Group 1 - AL-0 mg/kg/day Group 2 - AL-30 mg/kg/day Group 3 - AL-15 mg/kg/day
Group 4 - AL-7.5 mg/kg/day Group 5 - AL-3.75 mg/kg/day Group 6 - AS-0 mg/kg/day
Group 7 - AS-75 mg/kg/day Group 8 - AS-37.5 mg/kg/day Group 9 - AS-18.8 mg/kg/day
Group 10 - AS-9.4 mg/kg/day Group 11 - AE-25 mg/kg/day

Table 6

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Body Weight Summary: Range Finding Phase 2, Males

Bodyweights (grams)

Group Sex		Day numbers relative to Start Date									
		-1	1	2	3	4	5	6	7	15	23
1M	Mean	240.10	246.43	256.13	262.30	268.37	275.63	284.43	287.10	332.90	373.87
	S.D.	5.31	1.76	2.59	3.90	5.77	7.88	8.98	9.81	11.97	13.75
	N	3	3	3	3	3	3	3	3	3	3
2M	Mean	239.90	253.63	260.13	264.97	268.53	269.93	276.87	280.17	333.47	374.73
	S.D.	5.96	8.35	5.04	4.59	2.97	6.26	6.14	9.17	16.56	19.19
	N	3	3	3	3	3	3	3	3	3	3
3M	Mean	239.63	250.27	254.33	260.73	265.27	270.57	274.47	277.57	321.30	360.00
	S.D.	5.16	6.21	4.17	6.12	2.18	2.63	1.55	1.31	4.12	6.30
	N	3	3	3	3	3	3	3	3	3	3
4M	Mean	239.53	246.67	253.47	259.13	266.50	273.00	278.97	286.03	334.03	379.73
	S.D.	4.58	3.76	2.25	2.03	3.40	4.07	2.00	2.97	12.20	15.44
	N	3	3	3	3	3	3	3	3	3	3
5M	Mean	239.70	248.10	257.47	261.20	268.33	272.83	279.80	281.97	328.60	367.47
	S.D.	6.95	7.05	7.31	11.22	14.19	19.10	22.75	24.16	47.35	66.69
	N	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 6 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Body Weight Summary: Range Finding Phase 2, Males

Bodyweights (grams)

Group Sex		Day numbers relative to Start Date									
		-1	1	2	3	4	5	6	7	15	23
6M	Mean	239.77	245.67	253.97	258.83	264.23	270.00	275.90	279.37	322.70	360.17
	S.D.	5.00	4.92	4.16	5.18	4.78	4.50	2.25	2.93	4.78	2.07
	N	3	3	3	3	3	3	3	3	3	3
7M	Mean	237.10	241.87	246.17	248.47	250.27	255.53	257.10	265.23	312.40	356.30
	S.D.	4.42	6.22	9.68	6.44	7.74	8.10	5.40	4.48	9.88	11.48
	N	3	3	3	3	3	3	3	3	3	3
8M	Mean	240.23	247.13	250.17	256.97	264.23	269.07	273.77	272.47	331.33	370.43
	S.D.	4.90	5.73	4.80	5.59	11.32	10.54	12.43	13.45	23.59	28.59
	N	3	3	3	3	3	3	3	3	3	3
9M	Mean	240.30	247.73	254.43	261.50	266.47	271.23	278.10	281.70	330.20	368.97
	S.D.	4.93	6.18	5.93	5.37	7.46	7.57	9.79	11.08	21.96	28.07
	N	3	3	3	3	3	3	3	3	3	3
10M	Mean	239.47	245.70	250.00	254.97	261.93	265.23	270.63	278.57	329.70	371.80
	S.D.	4.61	6.26	9.56	11.69	15.50	15.04	14.59	17.65	27.54	30.44
	N	3	3	3	3	3	3	3	3	3	3
11M	Mean	242.17	250.97	258.87	265.10	271.13	274.27	279.10	287.03	338.13	382.67
	S.D.	6.56	7.21	8.44	9.46	11.55	15.06	15.72	17.39	27.33	42.77
	N	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 6 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Body Weight Summary: Range Finding Phase 2, Females

Bodyweights (grams)

Group Sex		Day numbers relative to Start Date									
		-2	1	2	3	4	5	6	7	15	23
1F	Mean	186.70	194.73	193.37	196.80	194.10	200.73	200.70	204.50	225.83	237.17
	S.D.	3.95	5.89	7.65	3.68	1.11	4.05	7.20	4.78	7.40	7.79
	N	3	3	3	3	3	3	3	3	3	3
2F	Mean	187.77	202.07	199.77	205.33	203.80	204.83	204.60	210.80	236.93	252.17
	S.D.	4.14	3.15	6.64	1.23	0.70	2.40	3.55	3.50	0.86	6.92
	N	3	3	3	3	3	3	3	3	3	3
3F	Mean	187.83	198.50	197.17	195.57	195.93	198.73	199.77	197.10	214.13	228.60
	S.D.	8.01	6.76	6.96	4.59	1.99	1.01	2.27	1.77	4.20	4.71
	N	3	3	3	3	3	3	3	3	3	3
4F	Mean	186.63	196.60	188.20	195.37	193.30	199.13	197.47	199.30	222.90	236.60
	S.D.	7.62	8.51	7.64	14.40	10.13	11.67	10.92	16.13	26.48	32.37
	N	3	3	3	3	3	3	3	3	3	3
5F	Mean	185.87	193.13	189.93	191.00	191.47	194.43	193.13	197.10	210.87	224.07
	S.D.	5.56	5.58	0.84	6.32	9.19	9.12	2.32	5.28	5.17	11.59
	N	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day Group 2 - AL: 37.5 mg/kg/day Group 3 - AL: 18.8 mg/kg/day
Group 4 - AL: 9.7 mg/kg/day Group 5 - AL: 4.7 mg/kg/day Group 6 - AS: 0 mg/kg/day
Group 7 - AS: 75 mg/kg/day Group 8 - AS: 37.5 mg/kg/day Group 9 - AS: 18.8 mg/kg/day
Group 10 - AS: 9.4 mg/kg/day Group 11 - AE 25 mg/kg/day
Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day Group 13 - AL/Lysine: 80 mg/kg/day
Group 14 - AS Vehicle: 0 mg/kg/day Group 15 - AS: 150 mg/kg/day

Table 6 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Body Weight Summary: Range Finding Phase 2, Females

Bodyweights (grams)

Group Sex		Day numbers relative to Start Date									
		-2	1	2	3	4	5	6	7	15	23
6F	Mean	186.37	202.57	203.33	202.20	202.30	212.20	210.37	208.63	230.73	245.50
	S.D.	10.14	8.62	9.39	14.95	6.07	14.39	13.98	16.87	25.61	21.96
	N	3	3	3	3	3	3	3	3	3	3
7F	Mean	187.53	190.13	186.50*	185.37	186.53*	189.70*	193.00	194.00	213.83	227.90
	S.D.	5.54	5.86	6.06	5.25	6.93	8.91	9.31	9.84	17.06	14.34
	N	3	3	3	3	3	3	3	3	3	3
8F	Mean	184.30	190.77	191.07	193.90	195.13	201.90	201.63	201.80	225.53	239.20
	S.D.	7.10	9.08	6.96	3.45	8.16	6.54	9.54	9.87	16.78	16.00
	N	3	3	3	3	3	3	3	3	3	3
9F	Mean	186.87	195.17	193.90	191.97	192.17	197.27	198.17	198.83	216.37	226.37
	S.D.	8.21	8.27	6.93	5.26	6.88	6.16	5.17	4.21	8.09	11.06
	N	3	3	3	3	3	3	3	3	3	3
10F	Mean	190.07	197.63	201.03	203.03	205.20	206.77	206.63	209.53	224.83	234.43
	S.D.	7.47	3.89	1.11	3.36	3.55	2.95	4.36	3.61	8.22	14.18
	N	3	3	3	3	3	3	3	3	3	3
11F	Mean	186.80	191.97	192.50	195.00	194.23	194.53	195.73	196.83	215.03	228.90
	S.D.	10.28	9.81	8.72	7.58	10.47	7.82	8.06	12.34	5.18	5.70
	N	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 6 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Body Weight Summary: Range Finding Phase 3, Males

Bodyweights (grams)

Day numbers relative to Start Date

Group Sex		-1	1	2	3	4	5	6	7	8	15	23
12M	Mean	239.73	252.47	258.37	266.97	273.10	280.60	284.57	290.83	297.17	.	.
	S.D.	4.54	6.69	6.93	10.27	10.21	12.34	13.18	13.30	16.85	.	.
	N	3	3	3	3	3	3	3	3	3	0	0
13M	Mean	237.00	251.00	228.03**	223.53**	223.30**	220.53**	228.03**	234.73**	242.20**	.	.
	S.D.	4.91	4.14	8.28	9.87	6.16	10.72	10.79	9.79	6.49	.	.
	N	3	3	3	3	3	3	3	3	3	0	0
14M	Mean	238.33	251.80	259.07	264.70	272.57	277.30	280.57	286.63	.	328.33	382.03
	S.D.	4.67	4.71	2.87	2.00	3.13	3.14	5.05	5.35	.	7.51	8.88
	N	3	3	3	3	3	3	3	3	0	3	3
15M	Mean	239.80	255.33	252.03	256.80	259.90	263.57	267.97	272.77	.	321.53	364.97
	S.D.	5.37	3.52	7.72	7.67	14.18	12.21	8.95	9.68	.	6.22	9.70
	N	3	3	3	3	3	3	3	3	0	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 6 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Body Weight Summary: Range Finding Phase 3, Females

Bodyweights (grams)

Day numbers relative to Start Date

Group Sex		-1	1	2	3	4	5	6	7	8	15	23
12F	Mean	203.50	213.90	213.20	212.17	220.63	220.70	221.27	222.90	232.37	.	.
	S.D.	5.54	3.18	5.96	5.51	8.78	6.66	3.07	6.22	8.40	.	.
	N	3	3	3	3	3	3	3	3	3	0	0
13F	Mean	203.53	218.43	203.23	201.47	208.63	192.37*	180.77**	185.03*	189.73*	.	.
	S.D.	7.62	10.35	9.03	9.28	7.50	11.05	12.90	13.13	16.90	.	.
	N	3	3	3	3	3	3	3	3	3	0	0
14F	Mean	202.77	212.03	212.23	213.23	219.10	219.03	221.33	222.60	.	239.77	258.47
	S.D.	8.65	9.25	9.56	11.82	10.10	9.92	8.48	11.59	.	16.30	22.05
	N	3	3	3	3	3	3	3	3	0	3	3
15F	Mean	201.37	206.97	199.50	193.10	190.90	185.00	193.75*	195.20	.	226.75	257.00
	S.D.	8.25	7.28	13.07	14.07	17.90	23.68	10.96	13.29	.	21.43	19.80
	N	3	3	3	3	3	3	2	2	0	2	2

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 7

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 2, Males

Day: 15 relative to Start Date

Group Sex		WBC 10^3/mm3	RBC 10^6/mm3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10^3/mm3	Retic %	Retic Count 10^5/mm3	Neut 10^3/mm3	Lymph 10^3/mm3	Mono 10^3/mm3	Eos 10^3/mm3
1M	Mean	16.797	7.187	14.47	42.93	59.80	20.13	33.67	925.7	3.77	2.697	2.247	13.830	0.287	0.137
	S.D.	5.327	0.332	0.29	0.55	2.36	1.12	0.55	58.0	0.40	0.162	0.623	4.396	0.125	0.031
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
2M	Mean	13.507	6.997	14.77	43.93	62.80	21.13	33.63	823.0	6.47	4.550	1.403	11.363	0.300	0.143
	S.D.	1.383	0.447	0.60	2.21	3.12	1.32	0.76	266.6	0.85	0.704	0.312	1.019	0.080	0.091
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
3M	Mean	11.670	6.703	14.23	42.53	63.50	21.23	33.43	866.3	5.97	4.000	1.510	9.617	0.247	0.083
	S.D.	2.279	0.240	0.25	0.80	2.08	0.67	0.06	108.3	1.02	0.580	0.815	1.379	0.055	0.058
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
4M	Mean	14.640	6.613	14.03	41.63	63.13	21.30	33.73	935.3	6.13	3.983	1.950	12.123	0.213	0.103
	S.D.	2.287	0.656	0.70	2.45	3.06	1.23	0.35	290.3	1.80	0.830	0.377	2.663	0.012	0.045
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
5M	Mean	14.450	7.410	15.03	44.67	60.33	20.30	33.67	987.0	4.10	3.000	1.700	11.980	0.333	0.123
	S.D.	1.430	0.469	0.35	1.60	2.15	0.92	1.10	145.3	2.03	1.396	0.580	1.252	0.119	0.032
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 7 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 2, Males

Day: 15 relative to Start Date

Group Sex		Baso 10^3/mm3	LUC 10^3/mm3
1M	Mean	0.163	0.137
	S.D.	0.104	0.055
	N	3	3
2M	Mean	0.147	0.153
	S.D.	0.047	0.060
	N	3	3
3M	Mean	0.083	0.123
	S.D.	0.035	0.059
	N	3	3
4M	Mean	0.100	0.147
	S.D.	0.017	0.025
	N	3	3
5M	Mean	0.167	0.147
	S.D.	0.006	0.031
	N	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day Group 2 - AL: 37.5 mg/kg/day Group 3 - AL: 18.8 mg/kg/day
Group 4 - AL: 9.7 mg/kg/day Group 5 - AL: 4.7 mg/kg/day Group 6 - AS: 0 mg/kg/day
Group 7 - AS: 75 mg/kg/day Group 8 - AS: 37.5 mg/kg/day Group 9 - AS: 18.8 mg/kg/day
Group 10 - AS: 9.4 mg/kg/day Group 11 - AE 25 mg/kg/day
Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day Group 13 - AL/Lysine: 80 mg/kg/day
Group 14 - AS Vehicle: 0 mg/kg/day Group 15 - AS: 150 mg/kg/day

Table 7(Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 2, Males

Day: 15 relative to Start Date

Group Sex		WBC 10^3/mm3	RBC 10^6/mm3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10^3/mm3	Retic %	Retic Count 10^5/mm3	Neut 10^3/mm3	Lymph 10^3/mm3	Mono 10^3/mm3	Eos 10^3/mm3
6M	Mean	12.913	7.400	14.70	44.17	59.63	19.83	33.27	1159.3	3.50	2.600	1.487	10.817	0.197	0.097
	S.D.	2.969	0.439	1.06	3.39	1.10	0.40	0.35	107.7	0.26	0.334	0.823	2.036	0.074	0.029
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
7M	Mean	16.530	7.153	14.87	44.60	62.37	20.77	33.30	1019.0	5.13	3.667	1.657	14.317	0.263	0.050
	S.D.	3.565	0.150	0.40	1.87	1.42	0.25	0.61	108.9	0.59	0.497	0.389	3.150	0.051	0.036
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
8M	Mean	14.007	7.123	14.60	43.53	61.27	20.53	33.57	1011.3	4.97	3.517	1.527	11.773	0.323	0.067
	S.D.	2.512	0.486	0.66	1.91	3.33	1.10	0.06	51.8	0.67	0.280	0.363	2.050	0.035	0.064
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
9M	Mean	14.067	6.853	13.90	42.70	62.30	20.27	32.53	1115.0	6.23*	4.263*	1.653	11.743	0.347	0.117
	S.D.	0.235	0.233	0.95	1.74	0.69	0.64	0.87	141.7	1.57	1.000	1.112	1.118	0.120	0.133
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
10M	Mean	15.560	6.920	14.67	44.33	64.03	21.23	33.17	1102.3	5.17	3.583	1.520	13.377	0.310	0.050
	S.D.	1.354	0.026	0.40	1.42	2.25	0.55	0.42	219.6	1.02	0.683	0.435	1.283	0.132	0.035
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
11M	Mean	16.887	7.053	14.20	43.30	61.47	20.20	32.80	1057.3	6.70**	4.700**	1.567	14.477	0.383	0.097
	S.D.	3.251	0.302	0.30	1.25	1.63	0.56	0.10	172.9	0.52	0.326	0.232	3.114	0.065	0.021
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day Group 2 - AL: 37.5 mg/kg/day Group 3 - AL: 18.8 mg/kg/day
Group 4 - AL: 9.7 mg/kg/day Group 5 - AL: 4.7 mg/kg/day Group 6 - AS: 0 mg/kg/day
Group 7 - AS: 75 mg/kg/day Group 8 - AS: 37.5 mg/kg/day Group 9 - AS: 18.8 mg/kg/day
Group 10 - AS: 9.4 mg/kg/day Group 11 - AE 25 mg/kg/day
Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day Group 13 - AL/Lysine: 80 mg/kg/day
Group 14 - AS Vehicle: 0 mg/kg/day Group 15 - AS: 150 mg/kg/day

Table 7(Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 2, Males

Day: 15 relative to Start Date

Group Sex		Baso 10^3/mm3	LUC 10^3/mm3
6M	Mean	0.140	0.177
	S.D.	0.026	0.086
	N	3	3
7M	Mean	0.127	0.123
	S.D.	0.021	0.021
	N	3	3
8M	Mean	0.140	0.173
	S.D.	0.026	0.055
	N	3	3
9M	Mean	0.073	0.133
	S.D.	0.012	0.006
	N	3	3
10M	Mean	0.130	0.167
	S.D.	0.036	0.075
	N	3	3
11M	Mean	0.170	0.203
	S.D.	0.044	0.097
	N	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day Group 2 - AL: 37.5 mg/kg/day Group 3 - AL: 18.8 mg/kg/day
Group 4 - AL: 9.7 mg/kg/day Group 5 - AL: 4.7 mg/kg/day Group 6 - AS: 0 mg/kg/day
Group 7 - AS: 75 mg/kg/day Group 8 - AS: 37.5 mg/kg/day Group 9 - AS: 18.8 mg/kg/day
Group 10 - AS: 9.4 mg/kg/day Group 11 - AE 25 mg/kg/day
Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day Group 13 - AL/Lysine: 80 mg/kg/day
Group 14 - AS Vehicle: 0 mg/kg/day Group 15 - AS: 150 mg/kg/day

Table 7 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 2, Females

Day: 15 relative to Start Date

Group Sex		WBC 10^3/mm3	RBC 10^6/mm3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10^3/mm3	Retic %	Retic Count 10^5/mm3	Neut 10^3/mm3	Lymph 10^3/mm3	Mono 10^3/mm3	Eos 10^3/mm3
1F	Mean	15.190	7.413	14.80	43.83	59.17	19.93	33.73	952.7	2.83	2.100	1.283	13.140	0.307	0.073
	S.D.	4.044	0.488	0.66	2.10	1.93	0.84	0.32	275.1	0.25	0.243	0.406	3.169	0.261	0.032
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
2F	Mean	12.977	6.910	13.70	42.30	61.17	19.83	32.40*	1203.0	4.50**	3.083**	1.113	11.447	0.167	0.060
	S.D.	2.023	0.598	1.04	3.91	0.47	0.21	0.44	174.9	0.52	0.068	0.510	1.887	0.031	0.020
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
3F	Mean	16.677	7.577	14.33	43.57	57.50	18.93	32.93	1153.3	4.23**	3.220**	1.973	13.967	0.240	0.123
	S.D.	2.100	0.183	0.40	0.93	1.41	0.38	0.31	307.4	0.06	0.098	0.693	1.506	0.072	0.021
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
4F	Mean	12.447	7.207	13.83	42.20	58.57	19.20	32.80	989.7	4.53**	3.267**	1.077	10.817	0.173	0.100
	S.D.	2.448	0.178	0.46	1.06	2.75	1.06	0.36	155.2	0.45	0.250	0.290	2.605	0.025	0.026
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
5F	Mean	12.967	7.460	14.00	42.47	57.07	18.80	32.97	852.3	3.60	2.683*	1.267	11.027	0.167	0.177**
	S.D.	3.171	0.635	0.80	2.16	2.08	0.72	0.65	107.2	0.17	0.330	0.699	2.537	0.058	0.025
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 7 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 2, Females

Day: 15 relative to Start Date

Group Sex		Baso 10^3/mm3	LUC 10^3/mm3
1F	Mean	0.150	0.233
	S.D.	0.095	0.186
	N	3	3
2F	Mean	0.093	0.090
	S.D.	0.051	0.056
	N	3	3
3F	Mean	0.157	0.217
	S.D.	0.015	0.006
	N	3	3
4F	Mean	0.123	0.153
	S.D.	0.029	0.076
	N	3	3
5F	Mean	0.130	0.210
	S.D.	0.010	0.140
	N	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 7 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 2, Females

Day: 15 relative to Start Date

Group Sex		WBC 10^3/mm3	RBC 10^6/mm3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10^3/mm3	Retic %	Retic Count 10^5/mm3	Neut 10^3/mm3	Lymph 10^3/mm3	Mono 10^3/mm3	Eos 10^3/mm3
6F	Mean	14.593	7.253	14.30	43.20	59.57	19.73	33.10	999.7	3.73	2.730	1.797	12.050	0.317	0.093
	S.D.	5.902	0.307	0.26	0.89	1.81	0.42	0.61	174.3	0.91	0.737	0.527	5.134	0.181	0.040
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
7F	Mean	15.780	7.190	13.80	41.97	58.40	19.20	32.83	924.7	5.23	3.797	3.760	11.343	0.193	0.180
	S.D.	4.504	0.355	0.66	1.68	2.55	0.61	0.50	131.1	2.46	1.869	1.837	2.597	0.064	0.252
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
8F	Mean	16.140	6.990	13.83	42.10	60.20	19.77	32.80	1099.7	5.03	3.527	1.270	14.170	0.247	0.143
	S.D.	3.597	0.078	0.50	1.51	2.10	0.76	0.10	154.4	1.53	1.029	0.252	3.644	0.035	0.038
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
9F	Mean	9.780	7.280	14.27	42.77	58.70	19.57	33.33	754.7	4.80	3.497	1.513	7.777	0.133	0.117
	S.D.	1.969	0.451	0.85	2.66	0.00	0.12	0.15	246.1	0.52	0.220	0.731	2.090	0.057	0.055
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
10F	Mean	13.237	7.273	14.17	42.37	58.33	19.50	33.43	924.3	3.07	2.237	1.190	11.530	0.147	0.090
	S.D.	4.855	0.434	0.25	0.64	2.80	0.85	0.32	30.9	0.23	0.188	0.439	4.687	0.072	0.026
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
11F	Mean	13.523	7.137	13.77	42.17	59.10	19.30	32.70	1028.7	5.00	3.553	1.123	11.737	0.297	0.137
	S.D.	1.594	0.343	0.67	1.88	0.40	0.10	0.17	103.5	0.20	0.071	0.301	1.742	0.162	0.055
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 7 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 2, Females

Day: 15 relative to Start Date

Group Sex		Baso 10^3/mm3	LUC 10^3/mm3
6F	Mean	0.093	0.137
	S.D.	0.023	0.074
	N	3	3
7F	Mean	0.123	0.180
	S.D.	0.040	0.026
	N	3	3
8F	Mean	0.127	0.183
	S.D.	0.025	0.040
	N	3	3
9F	Mean	0.080	0.160
	S.D.	0.010	0.182
	N	3	3
10F	Mean	0.127	0.150
	S.D.	0.070	0.089
	N	3	3
11F	Mean	0.103	0.123
	S.D.	0.040	0.012
	N	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day Group 2 - AL: 37.5 mg/kg/day Group 3 - AL: 18.8 mg/kg/day
Group 4 - AL: 9.7 mg/kg/day Group 5 - AL: 4.7 mg/kg/day Group 6 - AS: 0 mg/kg/day
Group 7 - AS: 75 mg/kg/day Group 8 - AS: 37.5 mg/kg/day Group 9 - AS: 18.8 mg/kg/day
Group 10 - AS: 9.4 mg/kg/day Group 11 - AE 25 mg/kg/day
Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day Group 13 - AL/Lysine: 80 mg/kg/day
Group 14 - AS Vehicle: 0 mg/kg/day Group 15 - AS: 150 mg/kg/day

Table 7 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 3, Males

Day: 8 relative to Start Date

Group Sex		WBC 10^3/mm3	RBC 10^6/mm3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10^3/mm3	Retic %	Retic Count 10^5/mm3	Neut 10^3/mm3	Lymph 10^3/mm3	Mono 10^3/mm3	Eos 10^3/mm3
12M	Mean	16.987	7.033	13.63	41.70	59.37	19.40	32.67	1063.0	4.50	3.167	2.820	13.520	0.287	0.103
	S.D.	1.405	0.172	0.32	1.25	3.04	0.95	0.45	209.7	0.95	0.722	0.589	1.568	0.081	0.081
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
13M	Mean	33.270	5.880	11.13	34.57	58.83	19.00	32.23	1124.0	7.33	4.390	10.787	21.083	0.653	0.163
	S.D.	7.845	0.633	1.11	3.58	0.93	0.52	0.42	513.9	2.41	1.873	4.333	4.999	0.116	0.127
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Group Sex		Baso 10^3/mm3	LUC 10^3/mm3
12M	Mean	0.070	0.183
	S.D.	0.010	0.040
	N	3	3
13M	Mean	0.203	0.377
	S.D.	0.050	0.170
	N	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 7 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 3, Males

Day: 15 relative to Start Date

Group Sex		WBC 10^3/mm3	RBC 10^6/mm3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10^3/mm3	Retic %	Retic Count 10^5/mm3	Neut 10^3/mm3	Lymph 10^3/mm3	Mono 10^3/mm3	Eos 10^3/mm3
14M	Mean	16.400	7.403	15.37	45.37	61.27	20.73	33.83	1288.7	3.47	2.553	2.230	13.623	0.237	0.063
	S.D.	1.521	0.127	0.25	0.76	1.15	0.51	0.21	337.3	0.38	0.275	0.895	1.262	0.101	0.031
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
15M	Mean	18.323	7.400	15.47	46.47	62.80	20.87	33.23	1013.7	5.07	3.757	2.857	14.853	0.283	0.050
	S.D.	0.359	0.235	0.76	2.02	1.35	0.38	0.60	122.0	0.83	0.522	0.692	0.711	0.083	0.026
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Group Sex		Baso 10^3/mm3	LUC 10^3/mm3
14M	Mean	0.073	0.177
	S.D.	0.023	0.099
	N	3	3
15M	Mean	0.100	0.177
	S.D.	0.035	0.072
	N	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 7 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 3, Females

Day: 8 relative to Start Date

Group Sex		WBC 10^3/mm3	RBC 10^6/mm3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10^3/mm3	Retic %	Retic Count 10^5/mm3	Neut 10^3/mm3	Lymph 10^3/mm3	Mono 10^3/mm3	Eos 10^3/mm3
12F	Mean	15.593	7.253	13.73	41.07	56.67	18.90	33.37	1062.7	3.50	2.553	1.647	13.427	0.197	0.113
	S.D.	3.026	0.226	0.21	0.90	2.24	0.35	0.74	205.9	0.10	0.116	0.488	2.490	0.032	0.025
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
13F	Mean	32.423	5.720	11.07	32.50	57.10	19.40	33.97	2058.7	3.03	1.490	8.460	22.240	0.920	0.193
	S.D.	5.868	1.033	1.92	4.98	2.65	0.78	0.70	239.5	3.80	1.629	4.681	4.683	0.234	0.223
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Group Sex		Baso 10^3/mm3	LUC 10^3/mm3
12F	Mean	0.073	0.137
	S.D.	0.025	0.035
	N	3	3
13F	Mean	0.163	0.447
	S.D.	0.065	0.150
	N	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 7 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Hematology Summary Report: Range Finding Phase 3, Females

Day: 15 relative to Start Date

Group Sex		WBC 10^3/mm3	RBC 10^6/mm3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	PLT 10^3/mm3	Retic %	Retic Count 10^5/mm3	Neut 10^3/mm3	Lymph 10^3/mm3	Mono 10^3/mm3	Eos 10^3/mm3
14F	Mean	18.483	7.820	15.80	45.77	58.50	20.23	34.57	1328.3	3.13	2.437	2.027	15.883	0.190	0.060
	S.D.	5.990	0.156	0.17	0.45	0.80	0.35	0.12	305.9	0.21	0.206	0.909	4.854	0.010	0.036
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
15F	Mean	21.295	6.215	13.10	39.40	63.40	21.15	33.35	1100.0	13.45	8.295	7.660	12.745	0.525	0.025
	S.D.	9.822	0.247	0.14	0.71	3.54	1.06	0.21	35.4	4.88	2.708	8.768	0.417	0.460	0.021
	N	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Group Sex		Baso 10^3/mm3	LUC 10^3/mm3
14F	Mean	0.093	0.233
	S.D.	0.059	0.129
	N	3	3
15F	Mean	0.095	0.245
	S.D.	0.021	0.177
	N	2	2

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 8

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Clinical Chemistry Summary Report: Range Finding Phase 2, Males

Day: 15 relative to Start Date

Group Sex		BUN mg/dL	Crea mg/dL	Gluc mg/dL	TP g/dL	Alb g/dL	Glob g/dL	A/G Ratio	NA mEq/L	K mEq/L	CL mEq/L	AST U/L	ALT U/L	ALP U/L
1M	Mean	16.17	0.53	121.3	6.57	4.20	2.37	1.80	144.7	6.53	97.7	90.7	53.7	326.3
	S.D.	0.67	0.06	1.5	0.21	0.26	0.12	0.20	1.2	0.12	0.6	7.6	3.5	42.3
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
2M	Mean	16.53	0.53	123.0	6.23	4.03	2.20	1.83	143.0	6.77	97.3	91.0	50.7	277.3
	S.D.	1.93	0.06	5.2	0.25	0.06	0.20	0.15	1.0	0.21	0.6	5.2	2.1	44.7
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
3M	Mean	15.67	0.53	118.0	6.13	4.00	2.13	1.90	143.7	6.87	98.3	79.7	55.7	275.7
	S.D.	1.23	0.06	4.4	0.06	0.10	0.12	0.17	0.6	0.29	0.6	6.4	2.1	19.1
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
4M	Mean	15.40	0.53	116.3	6.57	4.30	2.27	1.87	143.0	6.77	96.7	79.7	45.3*	326.3
	S.D.	1.25	0.06	8.5	0.38	0.30	0.15	0.15	0.0	0.12	0.6	4.7	3.1	23.0
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
5M	Mean	15.83	0.57	135.0	6.67	4.23	2.43	1.73	143.7	6.80	96.7	78.3	49.7	285.7
	S.D.	0.96	0.06	8.2	0.45	0.38	0.25	0.23	2.5	0.17	2.1	10.1	4.6	20.6
	N	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 8 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Clinical Chemistry Summary Report: Range Finding Phase 2, Males

Day: 15 relative to Start Date

Group Sex		BUN mg/dL	Crea mg/dL	Gluc mg/dL	TP g/dL	Alb g/dL	Glob g/dL	A/G Ratio	NA mEq/L	K mEq/L	CL mEq/L	AST U/L	ALT U/L	ALP U/L
6M	Mean	16.47	0.50	127.3	6.40	4.17	2.23	1.90	143.7	6.90	98.0	80.0	58.7	283.0
	S.D.	1.76	0.00	5.5	0.40	0.31	0.12	0.10	1.2	0.26	1.0	2.6	10.6	50.0
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
7M	Mean	14.43	0.50	125.3	6.27	4.20	2.07	2.03	143.3	6.60	97.3	92.3	64.3	351.7
	S.D.	0.85	0.00	2.3	0.23	0.10	0.15	0.15	1.5	0.17	0.6	14.4	4.7	16.9
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
8M	Mean	16.10	0.53	135.0	6.47	4.17	2.30	1.83	142.7	7.17	98.3	88.7	59.7	310.3
	S.D.	2.46	0.06	13.5	0.49	0.15	0.36	0.25	0.6	0.42	1.2	21.5	18.0	50.6
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
9M	Mean	15.97	0.50	125.7	6.33	4.07	2.27	1.80	144.0	6.93	98.7	77.3	48.0	220.7
	S.D.	2.08	0.00	9.9	0.38	0.23	0.15	0.00	1.0	0.15	1.5	4.9	7.0	23.2
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
10M	Mean	15.80	0.50	132.7	6.50	4.13	2.37	1.80	144.7	6.87	97.3	78.3	53.0	318.0
	S.D.	0.66	0.00	7.6	0.26	0.25	0.38	0.35	1.5	0.06	1.5	7.1	5.6	57.4
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
11M	Mean	14.33	0.57	135.0	6.33	4.03	2.30	1.77	143.7	6.87	97.7	78.0	54.7	333.7
	S.D.	2.00	0.06	14.4	0.23	0.12	0.20	0.21	1.2	0.23	0.6	1.0	1.5	120.7
	N	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 8 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Clinical Chemistry Summary Report: Range Finding Phase 2, Females

Day: 15 relative to Start Date

Group Sex		BUN mg/dL	Crea mg/dL	Gluc mg/dL	TP g/dL	Alb g/dL	Glob g/dL	A/G Ratio	NA mEq/L	K mEq/L	CL mEq/L	AST U/L	ALT U/L	ALP U/L
1F	Mean	17.57	0.53	116.3	7.20	4.90	2.30	2.13	144.0	6.20	98.0	88.3	55.0	183.3
	S.D.	3.55	0.06	5.7	0.10	0.10	0.20	0.25	1.0	0.60	1.0	11.9	5.3	41.3
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
2F	Mean	16.90	0.47	118.3	6.77	4.60	2.17	2.13	143.7	6.30	97.7	82.7	45.7	195.7
	S.D.	0.53	0.06	7.5	0.51	0.50	0.12	0.23	0.6	0.46	1.2	5.5	5.1	51.5
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
3F	Mean	19.57	0.60	108.3	7.10	4.87	2.23	2.23	145.0	6.20	101.0*	81.3	40.0	188.7
	S.D.	5.59	0.10	8.1	0.36	0.12	0.40	0.38	2.0	0.17	1.0	4.5	4.4	51.9
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
4F	Mean	16.67	0.57	113.0	7.03	4.80	2.23	2.17	143.0	6.13	98.7	81.3	52.7	175.0
	S.D.	2.64	0.06	2.6	0.21	0.26	0.15	0.21	1.0	0.42	1.5	4.0	9.5	65.0
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
5F	Mean	17.87	0.50	121.7	6.87	4.67	2.20	2.13	144.0	6.03	101.0*	83.7	42.0	156.3
	S.D.	3.35	0.00	3.5	0.32	0.23	0.10	0.06	1.7	0.15	1.0	17.6	7.5	25.1
	N	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 8 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Clinical Chemistry Summary Report: Range Finding Phase 2, Females

Day: 15 relative to Start Date

Group Sex		BUN mg/dL	Crea mg/dL	Gluc mg/dL	TP g/dL	Alb g/dL	Glob g/dL	A/G Ratio	NA mEq/L	K mEq/L	CL mEq/L	AST U/L	ALT U/L	ALP U/L
6F	Mean	19.23	0.57	106.3	7.23	4.97	2.27	2.17	144.0	6.17	99.7	82.7	54.7	228.7
	S.D.	1.44	0.06	15.3	0.50	0.42	0.12	0.15	1.0	0.45	2.1	4.7	12.6	39.7
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
7F	Mean	15.90	0.50	129.3*	6.87	4.63	2.23	2.10	144.3	6.03	99.7	78.0	45.3	202.0
	S.D.	1.66	0.00	7.6	0.49	0.15	0.38	0.36	1.2	0.21	2.1	6.0	5.0	36.6
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
8F	Mean	17.17	0.57	123.7	7.00	4.83	2.17	2.27	143.0	6.20	99.3	82.7	50.3	246.7
	S.D.	1.43	0.06	6.7	0.40	0.31	0.31	0.38	0.0	0.46	1.5	5.5	6.4	17.2
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
9F	Mean	15.37	0.57	124.3	6.93	4.57	2.37	1.93	143.7	5.67	99.7	84.7	49.7	210.7
	S.D.	0.12	0.06	3.2	0.40	0.31	0.15	0.12	1.2	0.06	0.6	10.4	5.7	39.3
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
10F	Mean	16.93	0.57	125.0	7.07	4.87	2.20	2.23	144.7	6.00	99.7	91.7	60.0	194.3
	S.D.	1.62	0.06	7.8	0.51	0.35	0.17	0.12	2.1	0.10	1.5	11.0	28.6	12.0
	N	3	3	3	3	3	3	3	3	3	3	3	3	3
11F	Mean	21.50	0.57	116.3	6.83	4.53	2.30	1.97	142.7	6.37	98.7	86.0	58.0	194.7
	S.D.	3.27	0.06	4.5	0.38	0.31	0.10	0.12	0.6	0.21	1.5	7.0	2.0	48.4
	N	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 8 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Clinical Chemistry Summary Report: Range Finding Phase 3, Males

Day: 8 relative to Start Date

Group Sex		BUN mg/dL	Crea mg/dL	BUN/Crea Ratio	Gluc mg/dL	TP g/dL	Alb g/dL	Glob g/dL	A/G Ratio	NA mEq/L	K mEq/L	CL mEq/L	AST U/L	ALT U/L	ALP U/L
12M	Mean	17.17	0.50	34.33	128.3	6.20	4.37	1.83	2.40	145.7	6.67	100.3	125.0	61.0	294.0
	S.D.	0.61	0.00	1.22	6.0	0.17	0.12	0.15	0.17	1.2	0.65	2.1	5.3	10.6	42.6
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
13M	Mean	15.80	0.53	29.90	132.0	5.87	3.37	2.50	1.40	142.7	6.37	98.3	111.7	51.0	231.0
	S.D.	2.69	0.12	1.66	18.2	0.45	0.12	0.36	0.17	1.5	0.67	2.9	25.5	5.6	38.0
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 8 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Clinical Chemistry Summary Report: Range Finding Phase 3, Males

Day: 15 relative to Start Date

Group Sex		BUN mg/dL	Crea mg/dL	BUN/Crea Ratio	Gluc mg/dL	TP g/dL	Alb g/dL	Glob g/dL	A/G Ratio	NA mEq/L	K mEq/L	CL mEq/L	AST U/L	ALT U/L	ALP U/L
14M	Mean	18.70	0.60	31.17	122.3	6.43	4.53	1.90	2.37	146.3	6.83	99.7	83.7	52.0	269.3
	S.D.	1.61	0.00	2.65	4.0	0.12	0.12	0.00	0.06	1.5	0.25	1.5	5.5	9.6	41.3
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
15M	Mean	17.03	0.53	32.10	113.3	6.63	4.60	2.03	2.27	146.7	6.87	99.0	100.0	58.0	278.3
	S.D.	0.67	0.06	2.59	5.0	0.29	0.10	0.21	0.21	1.5	0.32	2.0	9.5	7.5	36.9
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 8 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Clinical Chemistry Summary Report: Range Finding Phase 3, Females

Day: 8 relative to Start Date

Group Sex		BUN mg/dL	Crea mg/dL	BUN/Crea Ratio	Gluc mg/dL	TP g/dL	Alb g/dL	Glob g/dL	A/G Ratio	NA mEq/L	K mEq/L	CL mEq/L	AST U/L	ALT U/L	ALP U/L
12F	Mean	20.37	0.60	33.97	107.0	6.67	4.47	2.20	2.07	142.3	6.30	99.0	111.0	62.0	181.0
	S.D.	2.65	0.00	4.41	11.8	0.32	0.31	0.36	0.40	1.5	0.36	1.0	12.8	17.1	30.6
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
13F	Mean	28.53	0.83	33.63	119.0	6.17	3.30	2.87	1.17	143.7	6.60	98.7	105.3	51.7	131.0
	S.D.	13.32	0.25	7.38	22.5	0.06	0.30	0.31	0.25	2.5	1.21	2.3	19.6	12.3	9.2
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day; Group 2 - AL: 37.5 mg/kg/day; Group 3 - AL: 18.8 mg/kg/day; Group 4 - AL: 9.7 mg/kg/day; Group 5 - AL: 4.7 mg/kg/day; Group 6 - AS: 0 mg/kg/day; Group 7 - AS: 75 mg/kg/day; Group 8 - AS: 37.5 mg/kg/day; Group 9 - AS: 18.8 mg/kg/day; Group 10 - AS: 9.4 mg/kg/day; Group 11 - AE 25 mg/kg/day

Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day; Group 13 - AL/Lysine: 80 mg/kg/day; Group 14 - AS Vehicle: 0 mg/kg/day; Group 15 - AS: 150 mg/kg/day

Table 8 (Continued)

Dose-Range Finding Study of Injectable Artelinate and Artesunate in Rats

Clinical Chemistry Summary Report: Range Finding Phase 3, Females

Day: 15 relative to Start Date

Group Sex		BUN mg/dL	Crea mg/dL	BUN/Crea Ratio	Gluc mg/dL	TP g/dL	Alb g/dL	Glob g/dL	A/G Ratio	NA mEq/L	K mEq/L	CL mEq/L	AST U/L	ALT U/L	ALP U/L
14F	Mean	17.63	0.60	29.37	125.3	7.37	5.23	2.13	2.47	146.3	6.47	100.3	72.7	47.3	162.3
	S.D.	1.80	0.00	2.99	6.8	0.46	0.32	0.15	0.12	3.2	0.29	2.3	4.9	4.7	38.4
	N	3	3	3	3	3	3	3	3	3	3	3	3	3	3
15F	Mean	14.40	0.55	26.10	117.5	7.50	4.00	3.50	1.20	143.5	7.15	99.0	85.0	59.0	217.0
	S.D.	2.69	0.07	1.56	2.1	0.71	0.14	0.57	0.14	0.7	0.78	2.8	1.4	2.8	8.5
	N	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01; treated groups were compared to the appropriate control group (i.e., Groups 2-5 were compared to Group 1, Groups 7-10 to Group 6, Group 13 was compared to Group 12, and Group 15 to Group 14).

Nominal Dose: Phase 2: Group 1 - AL: 0 mg/kg/day Group 2 - AL: 37.5 mg/kg/day Group 3 - AL: 18.8 mg/kg/day
Group 4 - AL: 9.7 mg/kg/day Group 5 - AL: 4.7 mg/kg/day Group 6 - AS: 0 mg/kg/day
Group 7 - AS: 75 mg/kg/day Group 8 - AS: 37.5 mg/kg/day Group 9 - AS: 18.8 mg/kg/day
Group 10 - AS: 9.4 mg/kg/day Group 11 - AE 25 mg/kg/day
Phase 3: Group 12 - AL Vehicle: 0 mg/kg/day Group 13 - AL/Lysine: 80 mg/kg/day
Group 14 - AS Vehicle: 0 mg/kg/day Group 15 - AS: 150 mg/kg/day